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THE BACTERICIDAL ACTION OF PLEURAL EXUDATES

VII. STUDIES IN STREPTOCOCCUS INFECTION AND IMMUNITY *

FREDERICK P. GAY, M.D.

AND

ADA R. CLARK, M.A.

NEW YORK

The question of the precise methods by which the streptococcus infects animals under experimental conditions as introductory to more purposeful efforts to prevent and cure such infections has continued to interest the senior author actively for about seven years. A single pedigreed strain of the hemolytic *Streptococcus pyogenes* (Holman) has attained and retained a standard virulence for rabbits after passage (passage culture "H") through the pleural cavities of numerous animals, by which route its pathogenicity has become superlative, as compared with the original source culture (designated stock culture "H"), which has also been maintained in successive generations on rabbit blood agar without animal passage. The passage culture is also markedly more fatal in the pleura than elsewhere in the body.

The production of a generalized immunity, either active or passive, in rabbits against this culture, particularly when tested by the susceptible pleural route, remains hazardous and irregular; but throughout these studies we have met with phenomena which point to a relatively more effective protection in localized areas of the body, particularly the skin and the pleural cavity. Coincident with and, we believe, directly related to these conditions of local immunity, we have noted, in the case of pleural infections in which study of the cell contents of the exudate

*From the Laboratory of Bacteriology, Columbia University College of Physicians and Surgeons.

*Preceding studies in this series are: Gay, F. P., and Stone, R. L.: *J. Infect. Dis.* **26**:265, 1920. Gay, F. P., and Morrison, L. F.: *Ibid.* **28**:1, 1921. Gay, F. P., and Rhodes, B.: *Ibid.* **29**:217, 1921. Gay, F. P., and Rhodes, B.: *Ibid.* **31**:101, 1922. Gay, F. P.: *J. Immunol.* **8**:1, 1923. Gay, F. P., and Morrison, L. F.: *J. Infect. Dis.* **33**:338, 1923. Gay, F. P., and Clark, A. R.: *Ibid.* **36**:233, 1925.

is simple, an unusual outpouring of large mononuclear cells which by their characteristic response to vital or supravital staining are clearly identified as cells which have been successively denominated "clasmatocytes," "histiocytes" or "tissue macrophages."

It is not within our purpose, ability or intention to attempt to trace further the histogenetic origin of these cells, or to show their direct or indirect relationship to the monocytes of the blood or the endothelium of capillaries. These matters actively concern an increasing group of histologists, among whom may be mentioned Maximow,¹ Mallory,² Evans,³ Sabin,⁴ Cunningham,⁵ the Lewises,⁶ Foot,⁷ Permar,⁸ and McJunkin.⁹ Our interest extends simply to the identification of mononuclear cells in exudate or tissues which take trypan blue or neutral red in a characteristic manner and the relationship which these cells and possibly some of their allied forms (reticulo-endothelial system) may have to increased resistance and specific immunity to bacteria. And again our studies have so far been directed almost entirely to the streptococcus, as indicated by our introduction.

We have shown already (Gay and Morrison) that the injection of a substance like broth into the pleural cavity in a day provokes an exudate that is relatively rich in clasmatocytes, whereas after the same period aleuronat causes a relatively and actually large polymorphonuclear increase. In the first instance, the animal is protected; in the second, not at all. In all instances in which the clasmatocytes reached a total minimum (about 4 million in our experiments) in the pleural cavity, protection was assured against multiple lethal doses of streptococcus with the exception of instances in which too many polymorphonuclears were present, or in which the exudate was provoked by substances such as trypan blue, carbon or diatomaceous earth, in which the clasmatocytes are plugged with the irritating substances employed before the bacteria were injected. We have further indicated that recovery from intrapleural streptococcus infections in actively and passively immunized rabbits is associated with a clasmatocyte crisis in the pleural cavity (Gay and Morrison; Gay and Clark).

There is no difficulty in demonstrating under such conditions as have been mentioned that direct phagocytosis by clasmatocytes takes place;

1. Maximow, A. A.: *Arch. f. Micros. Anat.* **67**:680, 1906.
2. Mallory, F. B.: *J. Exper. Med.* **3**:611, 1898.
3. Evans, H. M., and Scott, K.: *Carnegie Inst. of Washington* **10**:48, 1921.
4. Sabin, Florence R.: *Physiol. Rev.* **2**:38 (Jan.) 1922.
5. Cunningham, R. S.: *Am. J. Physiol.* **59**:1 (Feb.) 1922.
6. Lewis, Margaret Reed: *Am. J. Pathol.* **1**:91 (Jan.) 1925.
7. Foot, N. C.: *J. M. Res.* **40**:353, 1919.
8. Permar, H. H.: *Am. Rev. Tuberc.* **9**:507 (Aug.) 1925.
9. McJunkin, F. A.: *Am. J. Path.* **1**:305, 1925.

in fact, it may be shown under appropriate conditions, such as we shall describe, that phagocytosis by clasmatoocytes in a mixed cell exudate is more active than phagocytosis by polymorphonuclears. In spite of repeated trials we were obliged to confess that all attempts at a crucial experiment, namely, destruction of streptococci by pleural exudates, whether predominatingly mononuclear or polymorphonuclear in content, *in vitro* have been failures. It is the purpose of this and a subsequent study to investigate more fully this apparent paradox and to consider more attentively the disposal of streptococci in pleural cavities that have been made relatively resistant or specifically immune.

The early discovery of a bactericidal power in exudates, particularly such exudates as contain considerable numbers of leukocytes, was naturally closely associated with the development of the phagocytic theory of immunity. Metchnikoff,¹⁰ throughout his work, had laid extreme and almost single importance on the activity of the polymorphonuclear white blood cells, whether in the blood stream, or extravasated into various areas of the body. Meanwhile, the German school of bacteriologists had pointed out the importance of bactericidal properties in the fluid elements of the body. A study of the exudates led to the first attempts to harmonize these two apparently divergent points of view, which have long since ceased to conflict, and may now be regarded as complementary. Of the many investigators who have studied the bactericidal effect of exudates and their constituent elements, we find that some have emphasized the importance of the living cells, notably Metchnikoff and his school, and others, beginning with the work of Buchner¹¹ and Schattenfroh,¹² have emphasized the importance of substances derived from the destruction of these cells.

It has been debated whether leukocytes eliminate bactericidal substances in the course of their normal existence, or, as Metchnikoff would prefer, whether such extracellular substances are artificial and produced as a result of destruction of the cells (phagolysis).

Among the earlier observers, Denys¹³ and his collaborators have taken an intermediate point of view, which we believe has since been largely overlooked; namely, that the destructive forces may be both within and without the cells. At all events, they pointed out conclusively a fact reiterated by other observers, that exudates, under certain conditions, were distinctively more bactericidal than blood serum. More

10. Metchnikoff, E.: *Immunity in the Infective Diseases*, Cambridge Univ. Press, 1905, p. 434.

11. Buchner, H.: *München. med. Wchnschr.* **41**:717, 1894.

12. Schattenfroh, A.: *Arch. f. Hyg.* **31**:1, 1897.

13. Denys, J., and Havet, L.: *La cellule* **10**:1, 1894. Denys, J., and Le Clef, J.: *La cellule* **11**:177, 1895.

concretely, a fact pointed out by Van de Velde,¹⁴ and later corroborated by Denys and Le Clef and Bordet,¹⁵ seems to have been entirely overlooked by subsequent investigators. This fact is that the supernatant cell-free fluid of exudates has in itself a considerable bactericidal property. The subsequent work, beginning with that of Buchner,¹¹ and extending through the observations of Schattenfroh,¹² Pettersson,¹⁶ Zinsser,¹⁷ Gengou,¹⁸ and many others has dealt largely with bactericidal substances that may be artificially extracted from leukocytes by various means.

Following the failure to obtain any striking practical results, such as seemed possible from the work of Hiss and Zinsser, interest has waned in the more theoretical aspects of this problem. It was with some hesitation, in view of the numerous opinions and conflicting results, that we recently approached this problem as a necessary prelude to understanding more fully the mechanism of the striking grade of protection that we have induced in rabbits as a result of modifications of the cell content of their exudates, in ways that we have already described.

As we have already stated, whole pleural exudates from rabbits, whether largely polymorphonuclear or clasmatoocyte in nature, fail to destroy minimal numbers of our streptococci of either stock or passage strain in the test tube. Such exudates may, however, destroy *Sp. cholerae* and *Bact. typhosum*, which two organisms we have considered less attentively as checks on our work on the destruction of the streptococcus.

In our previous experiments with pleural exudates we have contrasted the effect, in terms of protection, following the injection of 3 cc. of aleuronat starch, as compared with an equal amount of ordinary infusion broth without peptone. The pair were tested from eighteen to twenty-four hours later, at which time the contrast in differential cell counts and protection, that has been described, was apparent. To obtain larger amounts of exudate for study in vitro the technic has been modified, and with minor variations is as follows for the results here reported:

A. Polymorphonuclear Exudate: A rabbit is given 5 cc. of a sterile 5 per cent aleuronat plus 3 per cent starch in physiologic sodium chloride into the right (or sometimes both) pleural cavities. When removed, from eighteen to twenty hours later, an average of 9 cc. of exudate is found which is free from blood usually, if no vessel has been injured on injection and the animal thoroughly bled. The average differential and total counts of such exudates gave total numbers of each type of cells in the entire cavity in a series of twenty-five animals as follows:

14. Van de Velde, A.: La cellule **10**:401, 1894.

15. Bordet, Jules: Ann. Pasteur **11**:177, 1897.

16. Pettersson, A.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **7**:693, 1910.

17. Zinsser, H.: J. M. Res. **22**:397, 1910.

18. Gengou, O.: Ann. Pasteur **35**:497, 1921.

total white blood cells, 540,000,000; total polymorphonuclears 90 per cent, 486,000,000; total clasmatoocytes 10 per cent, 54,000,000.

B. Clasmatoocyte Exudate: The rabbit is given 5 cc. of sterile 40 per cent gum arabic in Ringer's solution mixed with an equal amount of 20 per cent beef extract in water. The exudate is obtained 68 to 72 hours later after exsanguinating the animal, and yields on the average 12 cc. of a brownish fluid, which has the disadvantage of clotting at times and being more frequently blood stained than the aleuronat exudate. The cell counts average (eighteen rabbits): total white blood cells, 152,000,000; total polymorphonuclears 21 per cent, 32,000,000; total clasmatoocytes 79 per cent, 120,000,000.

If the animals into which aleuronat is injected are allowed to live for three days, their exudate becomes mononuclear in type also, and they are protected; but the amount of fluid remaining in the cavity is too small to be useful for *in vitro* experiments.

To repeat our previous observations as modified here, it should further be stated that rabbits prepared the day previously by aleuronat are as susceptible as normal animals to intrapleural injection of passage "H" streptococcus, whereas the three day gum arabic broth animals are always protected against at least 200 lethal doses.

The passive transfer of the entire exudate of a well-protected gum arabic broth prepared animal to a normal rabbit does not protect the latter.

Protocol 1.—Rabbit 2012 was given 5 cc. of 20 per cent gum arabic broth containing 10 per cent beef extract on Oct. 2, 1925. Three days later the animal was bled and 23 cc. of exudate removed in paraffined tubes. The total number of cells in the cavity was 16,200,00 polymorphonuclears and 57,400,000 clasmatoocytes.

Twenty-one cubic centimeters of this exudate was injected with ± 65 minimal lethal dose passage Strept. "H" (1,300 colonies) into the right pleural cavity of normal rabbit 2013, which was found dead three days later with a typical sero-fibrinous pleurisy involving both cavities.

Such results suggest at least that the total number of leukocytes in the pleural cavity at the time of injection of the streptococcus does not suffice to account for the protection, but we know that new cells are continually arriving in such an inflamed area in the original animal. In anticipation, it may be stated that the simultaneous injection of the supernatant fluid of the exudate of a similarly prepared, protected animal, also fails to protect. It failed also when given in three doses of 6, 4, and 4 cc. at intervals beginning with the infecting dose.

RESULTS OF STUDY OF *IN VITRO* ACTIVITIES OF TYPE EXUDATES

Meanwhile, the study of the *in vitro* activities of our type exudates had yielded results of interest. The facts determined about the bactericidal effects of exudates may be categorically stated and then exemplified by typical protocols and further amplified.

1. As before stated, both polymorphonuclear and clasmatocyte exudates fail to destroy in 1 cc. amounts as few as 50 to 200 streptococci. Such a number of streptococci is chosen as well below the number that disappears from an aliquot portion of exudate in the protected (clasmatocyte) animal. Such amounts of exudate usually destroy much larger numbers of cholera vibrios and typhoid bacilli.

2. Continuous agitation of a mixture of exudate and streptococci in the manner suggested by Robertson and Sia¹⁹ also showed no destruction. In other words, absence of the mechanical agitation of respiration does not account for the failure of the exudate to work in vitro. If the exudate is removed through the diaphragm and retained under hydrocarbon oil (anaerobiosis), added streptococci are likewise unaffected.

3. If either of the type exudates is centrifugalized and the supernatant fluid removed, the latter does destroy streptococci in considerable numbers within twenty-four hours. It also destroys the other two organisms studied.

4. The supernatant fluid retains its bactericidal effect for streptococcus after heating to 56 C. for one-half hour, but loses its property of destroying cholera. It is inactivated for streptococcus also when heated to 73 C. for the same period; and also by Berkefeld filtration.

5. The cells washed after removal of the supernatant fluid and suspended in 25 per cent fresh rabbit serum in saline (which is inoffensive for streptococcus) will finally kill streptococci, in from forty-eight to seventy-two hours.

6. Extracts of both types of cells by freezing and thawing (Buchner), by the addition of dilute serum (Schneider²⁰) and most successfully by the addition of hydrochloric acid (Gengou¹⁸) are destructive within twenty-four hours for both streptococci and the other organisms.

7. Heating the acid extract of leukocytes to 56 C. for one-half hour does not destroy, but may diminish, its activity for streptococcus. It may destroy the property for killing cholera vibrios entirely.

8. In general, the supernatant fluids of aleuronat exudates and the corresponding extracts of polymorphonuclear cells are more active in aliquot parts than similar supernatants and extracts from clasmatocyte exudates. Correlatively should be mentioned the lower cell content of the clasmatocyte exudate, which accounts for this quantitative difference.

The following protocols illustrate the essential features enumerated above:

19. Robertson, O. H., and Sia, P. H. P.: *J. Exper. Med.* **39**:219 (Feb.) 1924.

20. Schneider, R.: *Arch. f. Hyg.* **75**:167, 1912.

Protocol 2.—(To illustrate points 1, 3, 4, 6). Aleuronat exudates were obtained in eighteen hours from two rabbits. When mixed they showed the following total count of cells per cubic centimeter: polymorphonuclears, 44,000,000; clasmatoocytes, 6,000,000.

Test tubes were prepared containing whole exudates or their fractions as designated, with a total volume of 1 cc. To such tubes were added 0.1 cc. of a dilution of 1:100,000 of a twenty-hour broth culture of stock streptococcus "H." With the stock culture utilized this amount contained fifty streptococci (or colonies). Streaks were made from each tube on blood agar twenty-four and forty-eight hours later.

	Result
1. Whole exudate 1 cc. plus stock streptococcus "H" 0.1 cc.	Growth 24 and 48 hours
2. Supernatant fluid 1 cc. plus stock streptococcus "H" 0.1 cc.	Sterile 24 and 48 hours
3. Supernatant fluid 56 C. 1 cc. plus stock streptococcus "H" 0.1 cc.	Sterile 24 and 48 hours
4. Supernatant fluid 73 C. 1 cc. plus stock streptococcus "H" 0.1 cc.	Growth 24 and 48 hours

(A.) To the sedimented cells of 4 cc. of exudate from which the supernatant has been removed, there is added 2 cc. of N/100 HCl and the mixture incubated for three hours at 37 C. and then left in the icebox overnight; then is added 2 cc. N/100 NaOH. A control solution (A') contains the N/100 HCl incubated, and to it is added N/100 NaOH. To both tubes is added 2 cc. of 10 per cent fresh rabbit serum, to serve as nutrient medium in the case of control. One and five-tenths cubic centimeters of the resultant extract "H" represents the extract of 1 cc. of cells.

	Result
5. Neutralized acid extract 1.5 cc. plus stock streptococcus "H" 0.1	Sterile 24 hours
6. Neutralized control 1.5 cc. plus stock streptococcus "H" 0.1	Growth 24 hours
7. Neutralized acid extract 56 C. plus stock streptococcus "H"	Sterile 24 hours
8. Neutralized control 56 C. plus stock streptococcus "H"	Growth 24 hours

Protocol 3.—(To illustrate point 5). Aleuronat exudate from rabbit 2271. Cells per cubic centimeter: polymorphonuclears, 61,200,000; clasmatoocytes, 4,600,000. Part of the exudate was divided by centrifugalization into supernatant and sedimented cells; the latter were washed in a 25 per cent dilution of fresh rabbit serum in physiologic sodium chloride and then suspended in a fresh portion of it. This dilute rabbit serum is also used as a control; 0.1 cc. of a dilution of stock streptococcus "H" (118 colonies) is added to each tube. Mixtures are made as follows with streaks on three successive days:

	One Day	Two Days	Three Days
1. Whole exudate 1 cc. plus streptococcus 0.1	Growth	Growth	Growth
2. Supernatant 1 cc. plus streptococcus 0.1	Sterile	Sterile	Sterile
3. Supernatant 0.5 cc. plus streptococcus 0.1	Sterile	Sterile	Sterile
4. Cell suspension 1 cc. plus streptococcus 0.1	Growth	Sterile	Sterile
5. Cell suspension 0.5 cc. plus streptococcus 0.1	Growth	Scant	Four colonies
6. Dilute serum control 1 cc. plus streptococcus 0.1	Growth	Growth	Growth
7. Dilute serum 0.5 cc. plus streptococcus 0.1	Sterile	Growth	Growth

It is evident from these results that, in the first place, streptococci and cholera vibrios differ in the manner in which they are destroyed by leukocytes and leukocyte products. This is notable, particularly in respect to the thermolability of the supernatant fluid in the destruction of cholera and its thermostability in reference to streptococci; in other words, in the case of the cholera vibrio, we have to do primarily with a sensitizer-alexin complex, whereas in the case of streptococcus we are

dealing with a different phenomenon, possibly analogous to one that has been described in connection with the bactericidal effect of serum on anthrax bacillus (Wilde²¹). We have actually demonstrated alexin in the fresh supernatant fluid repeatedly on adding sensitized blood cells, and even found traces of sensitizer for the cholera vibrio in the same fluid, but we do not wish at this time to enter further into a discussion of the mechanism involved here, but confine our discussion to the effect on the streptococcus.

The exudates as a whole, of both types, contain supernatant fluids which are destructive for streptococcus, and cells which through phagocytosis slowly destroy streptococcus. Both types of cells, moreover, yield extracts that are more rapidly destructive. There is every evidence that the bactericidal substance in the supernatant and that extracted from the cells are identical, and yet the presence of cells in the original exudate in some way prevents the action which the supernatant fluid alone possesses. It may actually be shown that continued contact for five hours at body temperature of the supernatant fluid with the cells in the exudate outside the body destroys or removes its bactericidal effect. This result is irrespective of the presence of streptococcus.

Our conviction was at first that the rapid disappearance of the streptococcus from the pleural cavities in protected animals (six hours in broth prepared animals and three hours in passively immunized animals) meant that destruction had taken place *in situ*, and by means of the specific action of one type of exudate (clasmatocyte) as compared with the other type (polymorphonuclear) which did not lead to sterilization. This conviction is probably erroneous, since, in the first place, the cell destruction of streptococcus which the supernatant possesses outside the body and which perhaps the whole exudate, through fluctuations in and replenishing of its constituent parts, might possess within the body, could not account for the rapid disappearance of the bacteria from the pleural cavity. In a simple broth prepared animal (previous work, Gay and Morrison) virulent streptococci have diminished in three hours and entirely disappeared from the pleural cavity in six hours. The supernatant fluid *in vitro* shows actual increase of bacteria for two or three hours, and complete sterilization may not be complete, although usually so, in twenty-four hours.

There is further disparity between *in vitro* and *in vivo* results in that the polymorphonuclear exudate contains more streptococidal elements outside the body, whereas only the animal with clasmatocyte exudate is protected. As we shall see in the following paper, reference to the underlying tissues from which the exudate is derived will explain more definitely the difference in results obtained in and outside the body,

21. Wilde, M.: *Ztschr. f. Hyg.* **37**:476, 1901.

but we shall at this point continue a discussion rather on the essential bactericidal properties which are inherent in fractions or extracts of the exudate, although not always evident in the exudate as a whole.

Among other points of interest is the fact that the bactericidal effect of the supernatant fluid is much more marked on the stock streptococcus than on its corresponding passage strain.

Protocol 4.—Supernatant of aleuronat exudate 2235 employed as in protocol 2. Varying dilutions of stock and passage "H" cultures were used in a total volume of 0.1 cc. so as to give varying numbers of streptococci as indicated in the protocol:

			One Day	Two Days
1.	Supernatant fluid 0.5 cc. plus stock streptococcus dilution 0.1	(60)	Sterile	Sterile
2.	Supernatant fluid 0.5 cc. plus stock streptococcus dilution 0.1	(6,000)	Sterile	Sterile
3.	Supernatant fluid 0.5 cc. plus stock streptococcus dilution 0.1	(60,000)	Sterile	Sterile
4.	Supernatant fluid 0.5 cc. plus stock streptococcus dilution 0.1	(600,000)	Scant	Sterile
5.	Supernatant fluid 0.5 cc. plus stock streptococcus dilution 0.1	(6,000,000)	Growth	Growth
6.	Supernatant fluid 0.5 cc. plus passage streptococcus dilution 0.1	(112)	Sterile	Sterile
7.	Supernatant fluid 0.5 cc. plus passage streptococcus dilution 0.1	(11,200)	Growth	Growth
8.	Supernatant fluid 0.5 cc. plus passage streptococcus dilution 0.1	(112,000)	Growth	Growth
9.	Supernatant fluid 0.5 cc. plus passage streptococcus dilution 0.1	(1,120,000)	Growth	Growth

In this experiment at least 500 times as many stock, "H", streptococci were killed as passage, "H", by the same amount of fluid. This is an interesting comment on the nature of virulence. It is well known that virulent bacteria repel leukocytes, whereas nonvirulent strains attract them (Bordet); but we have here evidence rather of a superior resistance of the virulent strains to the bactericidal extracts of leukocytes.

The thermostabile destructive element in the fluid of exudates which destroys streptococcus is not absorbed or used up by the first dose of organisms that it destroys. Thus it may be shown that streptococci in the dose we have usually employed (50 to 150 colonies) may be added on successive days to a cubic centimeter of supernatant and regularly destroyed for at least nine days. Such repeated inoculation finally gives a positive culture, thus showing that the supernatant fluid does not lack the qualities of a culture medium.

Heating the whole exudate to 56 C. for one half hour does not destroy the bactericidal power of the subsequently derived supernatant fluid or the cell extract. The whole heated exudate, however, is still nonbactericidal. Since heat to this degree destroys the phagocytic property of leukocytes, the segregation and protection of streptococci from destruction by the ambient fluid cannot be invoked to explain the action of whole exudate. Rabbit serum heated to 56 C. also inhibits the action of the supernatant fluid, although fresh serum does not. Clotting of the exudate removes the bactericidal property from supernatant and, also, as we have mentioned, continued standing of the cells with the supernatant. We would, then, appear to be dealing with some colloidal phenomenon and not with the occurrence of phagocytosis.

SUMMARY

In this study are described the streptococcal properties of pleural exudates from rabbits purposely varied to include relatively different proportions of polymorphonuclear cells and mononuclear cells (clasmatocytes). The presence of the mononuclear exudate in the pleural cavity is coincident with protection of the animal. Neither of these exudates is in its entirety bactericidal outside the animal body. The simple transfer of such an exudate to a normal animal also fails to protect the second animal. Experiments *in vitro*, then, with these exudates, do not explain conditions as they exist in the body.

Although whole exudates of both cell types are not destructive to the streptococcus, they do destroy some other organisms. Furthermore, the supernatant fluid of either exudate will destroy the streptococcus. The cells themselves from either exudate may slowly destroy the streptococcus, and an acid extract of either type of cell destroys the streptococcus readily. The streptococcal property of fractions of exudates is thermostable, whereas the corresponding property for some other bacteria is thermolabile.

A following paper is designed to explain the discrepancy between the results obtained within and without the body.

A HISTOLOGIC BASIS FOR LOCAL RESISTANCE AND IMMUNITY TO STREPTOCOCCUS

VIII. STUDIES IN STREPTOCOCCUS INFECTION AND IMMUNITY *

F. P. GAY, M.D.

A. R. CLARK, M.A.

AND

R. W. LINTON, M.A.

NEW YORK

In the preceding article, we have shown that neither a pleural exudate from rabbits that is largely polymorphonuclear in character and indicates lack of protection of the animal, nor an exudate which is largely clasmatoctytic from a protected animal in its entirety possesses any bactericidal property for streptococcus in vitro. The supernatant fluid from such exudates, the acid extracts of the washed leukocytes, and, more slowly, the washed leukocytes themselves, are able to destroy small numbers of streptococcus. These extracorporeal bactericidal phenomena fail to explain what goes on in the body. In the first place, sterilization is more rapid in the body, and in the second place, in the presence of a polymorphonuclear exudate the body does not become sterile; whereas such an exudate contains more bactericidal properties outside the body than the clasmatoctyte fluid.

We turn again to a more intensive consideration of what occurs when streptococci are injected into the pleural cavities of normal, aleuronat prepared, broth prepared, and specifically and locally immunized rabbits.

Our earlier experiments (Gay and Morrison¹) seemed to indicate, not only that there was a direct relation between a proportionately high clasmatoctyte count in the pleural cavity and protection, but that a minimal number of such cells was essential for such protection. And yet actively immunized pleural cavities, in which little or no exudate was present and, consequently, few clasmatoctytes, were highly protected. Extended experience shows that whereas the nature of the exudate and the total number of clasmatoctytes may indicate protection, such evidence is merely reflective of underlying tissue changes, and further evidence shows that the material employed to produce an exudate is less important than the time element involved. The local influx of polymorphonuclear cells is known to be one of the initial phases of inflammation, whether septic or aseptic in character; following this phase, mononuclear cells

* From the Laboratory of Bacteriology, Columbia University College of Physicians and Surgeons.

1. Gay, F. P., and Morrison, L. F.: J. Infect. Dis. **33**:338-367, 1923.

arrive with a varying rapidity which depends markedly on the virulence of the organism employed.

Attention is called to the fact that the present method of producing exudates, as described in the preceding article, differs from the one employed previously (Gay and Morrison¹), and although the main protection results are in agreement, the cell counts differ. The preceding article should be consulted for the exact methods employed in the preparation of cavities outlined in this work.

In table 1 are given the results in terms of protection against streptococcus obtained by previous injection at varying time intervals of the two materials we have used, together with coincident cell counts.

These cell counts represent averages based in each instance on from three to twenty-one animals which were killed after preparation and without infection. The results in the way of protection were based in each instance on the infection of several animals.

TABLE 1.—*Pleural Exudates in Normal and Prepared Rabbits in Relation to Total Cells Present and to Protection. Various Time Intervals.*

Preparation	Time, Hours	Fluid, Cc.	Total Clasmato-cytes	Total Polymorpho-nuclears	Protec-tion
Control.....	..	0.2	300,000	50,000	None
Aleuronat-starch.....	18	9	54,000,000	480,000,000	None
Aleuronat-starch.....	48	4	161,000,000	735,000,000	None
Aleuronat-starch.....	72	2	51,000,000	72,500,000	Protected
Gum arabic broth.....	18	15	49,000,000	566,000,000	None
Gum arabic broth.....	48	12	177,000,000	106,000,000	None
Gum arabic broth.....	72	12	120,000,000	32,000,000	Protected

The protection here evidenced is related, not directly to the number of clasmatocytes, but rather to the presence of a sufficient number of clasmatocytes in the presence of a properly diminished number of polymorphonuclear cells. The volume of exudate is apparently not a factor of importance as judged from these figures, but, as we shall see later, has a bearing on the rapidity of sterilization of the cavity.

For the sake of contrast we shall deal largely with the extremes of the exudate type, namely, a polymorphonuclear exudate (eighteen hour aleuronat starch) and a clasmatocyte exudate (seventy-two hour gum arabic broth). It is evident from this table why, although aleuronat starch will produce protection in seventy-two hours as well as gum arabic broth, the latter fluid was chosen for comparative study *in vitro*; it contains both absolutely and relatively a larger number of clasmatocytes in the greater volume of exudate.

NORMAL STRUCTURAL RELATIONSHIPS IN THE RABBIT PLEURA

The pleural cavity is lined with a serous membrane which covers lung, parietal pleura and diaphragm. It consists of a single layer of flat serosal cells which, so far as can be observed with ordinary staining

methods, are continuous, although the question of actual stomata between the cells has been raised. Under this single cell lining is found a layer of fibrous elastic tissue which in the rabbit at least varies considerably in thickness increasingly from lung to diaphragm, to intercostal (parietal) pleura. On the visceral surface the respiratory epithelium of the peripheral alveoli seems to lie directly adjacent to the pleural serosa, except where the interalveolar or interlobular septums run down from the surface. On the diaphragm a thin layer of elastic fibrous tissue with scant nuclei separates the serosa proper from the muscle fibers. The total pleural membrane measures here about 24 microns. Over the

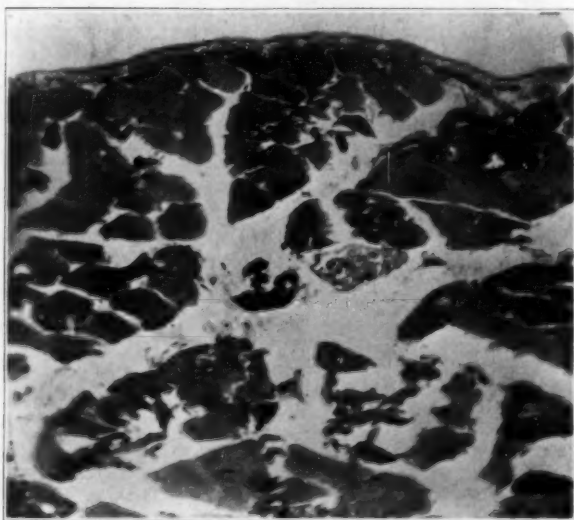


Fig. 1 (Rabbit 1487).—Normal parietal pleura of rabbit. Single layer of serosal cells with subserosal layer composed mostly of collagen fibrils with few nuclei. Average width of pleural layer, 27 microns; $\times 120$.

intercostal muscles the subserous layer of the pleura is the thickest, but contains few nuclei and numerous collagen fibrils lying in various directions (fig. 1). The entire layer measures on the average 28 microns in thickness (five animals). For purposes of histologic study, sections of this parietal pleura have been cut uniformly between the 6th and seventh ribs and somewhat posteriorly.

We have had occasion previously to discuss the question of pleural drainage (Gay and Rhodes²) and came to the conclusion that, so far as the superficial layer of the lung is concerned, it is directed away from the hilum toward the pleural network (Miller³). This assumption fits

2. Gay, F. P., and Rhodes, B.: *J. Infect. Dis.* **29**:217, 1921.

3. Miller, W. S.: *Am. J. Roentgenol.* **4**:269-279, 1917.

in with our previous experience with experimental streptococcus pneumonia which could regularly be produced by intrabronchial insufflation, and which invariably was followed by empyema. On the other hand, the experimental empyema, as we have ordinarily produced it by direct intrapleural inoculation, never involves the lung tissue. These observations were checked by the histologic and bacteriologic proof of the presence and extension of streptococci in the first process in the lungs and into the pleura, and their sharp delimitation to the pleural exudate in the latter instance.

Our present study extends these observations by showing that various pigments and bacteria injected into the pleural cavity are removed from it entirely through the intercostal and diaphragmatic surfaces and not through the lungs. The lymphatics of these areas drain into the mediastinal nodes according to the best anatomic evidence we can find (Delamere⁴), and in full agreement with our work and the observations of Karsner and Swanbeck.⁵

If a 10 per cent suspension of "Norit" (purified vegetable charcoal) or of a 3 per cent suspension of Higgin's ink is injected into the pleural cavity in an amount of 2 or 3 cc. and the animal is killed two days later, accumulations of pigment-bearing "clasmatoocytes" are found in nodules or masses under the serosal layer of the diaphragm and parietal pleura, but none in a similar position in the lung. One per cent trypan blue gave the same result, in which case the clasmatoocytes lining the sinuses of the superior retrosternal lymph nodes are also selectively filled with dye. That this localized staining which omits the lung tissue is not due to absence of clasmatoocytes in the lungs is shown by a more intensive saturation of the animal by seven to ten daily injections of dye into the peritoneum or the blood stream; here a few clasmatoocytes can be found under the serosal layer of the lung as well as in the parietal layer. The significance of this drainage current will be seen when we come to discuss the disposal of bacteria from the pleural cavity.

EFFECT OF ALEURONAL-STARCH INJECTION INTO THE PLEURAL CAVITY

Histologic preparations have been studied from a number of different animals, most of them killed at the critical period (eighteen to twenty hours) after injection, as used for the study of exudates and protection. The changes are uniformly more marked and advanced in the intercostal pleura and diaphragm than in the lung.

4. Delamere, G.: *The Lymphatics*, in Poirier and Cunes: *Anatomy*, English trans., Constable & Co., 1913.

5. Karsner, H. T., and Swanbeck, C. E.: *J. M. Res.* 42:91-98, 1920

The changes in the parietal pleura are already well marked at ten hours, and are evidenced by an increase in the width of the layer which at this period has reached 49 microns or nearly twice normal, and continues to an average of 63 microns at eighteen hours. The layer of serosal cells is broken in places, owing to the large accumulation of polymorphonuclear cells in the subserous layers (fig. 2) and the extreme congestion of the blood vessels. Small masses of aleuronat are found embedded in the wall. The serosal cells are swollen and stain irregularly. The polymorphonuclear cells are seen with elongated nuclei, passing between the serosal cells into the pleural cavity. Similar, though less



Fig. 2 (Rabbit 1371).—Parietal pleura of rabbit eighteen hours after injection of aleuronat starch mixture into pleural cavity. A small fragment of aleuronat lies under lining layer of serosal cells. Subserous layer is infiltrated with numerous polymorphonuclear leukocytes. Total width of pleura averages 64 microns. No protection against infection with streptococcus; $\times 120$.

marked, changes are evident in the diaphragm. In the lung, congestion of the superficial vessels is evident with thickening of the pleural layer, but notably fewer polymorphonuclears are found.

By the third day the parietal pleura has increased to a thickness which varies considerably but which averaged 140 microns in three animals, that is, five times normal (fig. 3). The serosal layer is intact. Under the serosal cells is a dense layer of rounded and elongated mononuclear cells. These cells extend deep down between the muscle fibers and collect about blood vessels in compact nodules. Few polymorphonuclears remain.

INJECTION OF STREPTOCOCCI INTO ALEURONAT PREPARED CAVITIES

New and extensive studies have been made of the fate of streptococci injected into the pleural cavities of rabbits prepared in the ways we have mentioned, and at various times previously. These studies have been paralleled by study of the histologic changes.

Both stock and passage cultures of streptococcus "H" have been employed for these injections, and more or less complete series as regards time intervals after injection have been secured. Separate animals are killed at intervals, since aspiration, through the complication of hemorrhage and incompleteness of data, is unsatisfactory. The stock cultures have been administered in large though nonfatal amounts, for the purpose of ascertaining the numbers and location of the organisms in the exudate and tissues. The doses have varied from 1 to 5 cc. of a twenty-

TABLE 2.—*The Study of Exudates from a Series of Rabbits Prepared by Injection of Aleuronat Starch Followed Eighteen Hours Later by a Large Dose of Stock Streptococcus "H" 125 to 400 Million Organisms in 1 Cc.*

Rabbit No.	Interval after Injection	Total* Clasmato-cytes in Pleura in Millions	Total* Polymorpho-nuclears in Millions	Cultures,† Percentage	Phago-cyte Clasmato-cytes, Per-centage	Phago-cyte Polymor-pho-nuclears, Per-centage	Bacteria in Cells, Per-centage	Extra-cellular Bacteria, Per-centage	Bacteria Unac-counted For,‡ Percentage
Control average...		54	486
2029	12 min.	76	372	1.0	64	15	48	3	49
2020	30 min.	118	590	0.1	43	6	41	1.3	57.7
2027	135 min.	85	1,794	0.034	57	4	60	4	84
2266	360 min.	83	954	0.16
2036	22 hr.	75	501	24 colonies†	0	0	15	0	85

* Estimated from total and differential count by multiplying by volume of exudate found in the cavity.

† Percentage of original numbers injected or actual number when nearly sterile.

‡ In relation to number injected.

† Of three other rabbits two were sterile and one gave 8 colonies.

four hour broth culture, usually the smaller amount, which contains from 125 to 300 million streptococci.

The passage culture has been used in two amounts; a small dosage of a dilution of the usual broth culture designed to contain from 3,000 to 4,000 organisms which represents from 100 to 200 lethal doses for the normal or the twenty-four hour aleuronat animal, and to which amount the seventy-two hour broth or aleuronat animal is resistant. In another series we used doses of 1 cc. of passage culture representing about 5 million lethal doses for the normal animal and easily fatal for the seventy-two hour broth animal as well.

The general results obtained in the aleuronat prepared cavities may be summarized as follows and illustrated with abbreviated protocols.

When large numbers of stock streptococci were injected into an eighteen hour prepared aleuronat cavity, the following changes occurred in the exudate (table 2):

The leukocytes showed a temporary fall on the part of the polymorphonuclear cells in twelve minutes, although the clasmatocytes made a slight increase. This was followed from thirty minutes onward through the first six hours by an increase of both types of cells, which reached three times the original number at the time of injection. There was a return to the original point at the end of twenty-four hours. The streptococci diminished rapidly, and cultures were usually sterile in twenty-four hours. The drop in the number of organisms was most notable perhaps in the first twelve minutes, at which point only about



Fig. 3 (Rabbit 3117).—Parietal pleura seventy-two hours after injection of aleuronat starch mixture. Markedly thickened pleura measures 266 microns; infiltrated with mononuclear cells; serosal cells swollen; $\times 120$.

one half of the original number injected were found in smears, and only an insignificant number remained alive. During the early periods, from twelve to thirty minutes, phagocytosis on the part of the clasmatocytes was very active, although there was a disproportionate number of polymorphonuclears present, approximately eight times as many. Six times as high a percentage of clasmatocytes as of polymorphonuclears were phagocytic. In twelve minutes fifty times as many organisms were seen on studying stained preparations⁶ of the exudates as could be cultivated,

6. Gram stains have been used to estimate extracellular bacteria and phagocytosis in addition to the Wright stain used for differential counts.

and in one-half hour, only 1 in 400 of those seen in cells occurred in culture, whereas of those outside cells something like 1 to 250 were viable. Although for simplicity not included in the table, separate estimates were made of the number of viable bacteria in the supernatant fluid and the cell deposits from exudates. In other words, there apparently had been an extraordinary and rapid destruction of the bacteria in the exudate itself in addition to the disappearance of something like half the number of organisms within the first thirty minutes.

If small though fatal amounts of passage culture streptococcus "H" are injected into rabbits, eighteen hours after preparation with aleuronat, the picture is quite different from that just described (table 3). The cells increased markedly from thirty minutes to six hours and then decreased at twenty-four hours, these changes being almost entirely on the part of the polymorphonuclear cells. A steady increase of the number of bacteria injected was evident from the first half hour;

TABLE 3.—*The Study of Exudates from a Series of Rabbits Given a Small Dose of Passage "H" (3,250 Streptococci) Eighteen Hours After Aleuronat Starch Mixture*

Rabbit No.	Interval after Injection	Total Clasmato-cytes in Pleura in Millions	Total Poly-morpho-nuclears in Millions	Cultures	Phago-cyte Clasmato-cytes, Percentage	Phagocytic Poly-morpho-nuclears, Percentage	Bacteria in Cells	Extra-cellular Bacteria
3105	30 min.	62	1,186	× 4	None	None
3106	120 min.	117	947	× 10	None	None
3107	300 min.	51	1,129	× 2,880	None	None	× 3,283
3108	24 hr.	37	302	× 62,492	21	8	× 11,815	× 59,630

4 times the original number injected were present at this period, 10 times the number in two hours, 3,000 times the number in six hours and more than 60,000 times the number at the end of twenty-four hours. No phagocytosis was evident at first on account of the small number of bacteria present, but by six hours, in the continued absence of phagocytosis, approximately the same number of bacteria could be counted in stained preparations outside the cell as were cultivated. A slight phagocytosis, mostly on the part of the clasmatocytes, was evident in twenty-four hours, but cultures evidenced the fact that nearly all the bacteria were viable, both within and without the cells.

Following the injection of stock streptococci in large amounts as outlined above, it was found that the parietal pleura had undergone an essential change within the earliest period of twelve minutes. Practically all the polymorphonuclear cells that in a prepared animal had been found infiltrated in the thickened pleura had disappeared, doubtless supplying the increase in the exudate which followed from this period on. These cells were evidently replaced to some extent in animals killed

one-half hour after injection of bacteria, and during this and the two hour period polymorphonuclears were evident in transit between the serosal cells in some sections of the pleura. Bacteria were found within the mononuclear cells lying under the serosal layer (fig. 7 illustrates a similar process from an immune animal). Whether these bacteria had been destroyed in situ or brought in by the phagocytes through the serosal layer, is not clear. We are inclined to the former hypothesis.

When small but fatal doses of passage streptococci, as outlined above, are given to similarly prepared aleuronat animals, the histologic changes noted are different. The polymorphonuclear cells may diminish slightly in the one-half hour period, but not so notably as in the animal given large amounts of stock culture. Hemorrhage is quite a prominent feature. At the end of two hours, the pleura was found fragmented and necrotic, the serosa entirely gone and the polymorphonuclear cells scattered and not numerous. The mononuclear cells were still present in very small numbers and were better preserved than the polymorpho-

TABLE 4.—*The Study of Exudates from a Series of Rabbits Given a Small Dose of Passage Streptococcus (4,000) Seventy-Two Hours After Injection of Aleuronat Starch*

Rabbit No.	Interval After Injection	Total Clasmato- cytes in Pleura in Millions	Total Poly- morphonuclears in Millions	Cultures
Control average.....		51	73
3117	120 min.	193	346	Sterile
3118	300 min.	88	543	Sterile
3119	24 hr.	24	23	16 colonies

nuclears. The picture was not essentially changed in six hours. At twenty-four hours, the pleura was found entirely necrotic, with nothing but the débris of nuclei on the surface of the muscles, among the bundles of which the polymorphonuclear cells had accumulated.

It will be recalled from table 1 that seventy-two hours after aleuronat injection the small amount of exudate present (2 cc.) contained nearly equal numbers of clasmatocytes and polymorphonuclear cells. At that period animals are found to be protected against at least 100 to 200 lethal doses. Following injection of passage culture, there was a remarkable increase in the number of both types of cells in the cavity, which reached in two hours four times the number originally present (table 4). Coincidentally there was an increase in the amount of fluid at two and six hours of two or three times the amount on injection. Cultures from the cavity were sterile at two and six hours, although in the single animal killed at twenty-four hours, a few scattered colonies were found (estimated as 16 in the entire cavity). With the small number of organisms employed, there was a rapid disappearance, and no bacteria

were visible in stained preparations at any time. The histologic preparations from animals of this sort showed no notable changes over the picture described for the prepared but uninoculated cavity.

If large amounts of passage culture designedly chosen to demonstrate phagocytosis, although unquestionably fatal, were injected, the following changes were noted (table 5): There was a rapid increase in the exudate and in the number of polymorphonuclear cells through the twenty-four hour period. The exudate increased as much as eight times the original amount and the cells more than ten times. The cell increase was due entirely to an increase in polymorphonuclears, the clasmatoocytes becoming distinctly diminished in from one to six hours, although nearly regaining their original number in twenty-four hours. During the first six hours there was a marked diminution in the number of bacteria which reached as low as 0.1 per cent of the total number

TABLE 5.—*The Study of Exudates from a Series of Rabbits Given a Large and Fatal Dose of Passage Streptococcus (140 to 160 Million) Seventy-Two Hours After Preparation with Aleuronat Starch*

Rabbit No.	Interval after Injection	Total Clasmatoocytes in Pleura in Millions	Total Polymorphonuclears in Millions	Cultures, Percentage	Phagocytic Clasmatoocytes, Percentage	Phagocytic Polymorphonuclears, Percentage	Bacteria in Cells, Percentage	Extracellular Bacteria, Percentage	Bacteria Unaccounted For, Percentage
Control average...		51	73
3115	60 min.	27	38	0.1	36	0	15	0.3	84.7
3123	120 min.	7	164	1.0	40	0.4	4	1	95
3122	360 min.	17	383	0.2	65	0	26	1	73
3121	24 hr.	43	1,003	×40.0	25	2	21	×19	..

injected, although at twenty-four hours there was a jump to forty times the original number. Phagocytosis in the early stage in the exudate was almost entirely on the part of the clasmatoocytes. In the two hour animal only were phagocytic polymorphonuclears seen.

The histology of the pleura in the animals with the large and eventually overwhelming doses of passage culture differed notably from the one obtained with the sublethal injection. In sections obtained in two and six hours there was marked hemorrhage into the pleura and infiltration of the polymorphonuclear cells. Although the serosa was swollen and detached, the deeply lying mononuclear cells were well preserved and showed none of the evidences of extreme necrosis visible at this period in the early aleuronat prepared animals. In addition, in the six-hour preparation phagocytosis on the part of the mononuclear cells lying in the granulation tissue was observed. In the twenty-four hour animal the architecture of the tissue was still evident, although the number of poorly staining cells with pyknotic nuclei was increased and small areas of necrosis were evident.

EFFECT OF INJECTION OF GUM ARABIC BROTH INTO
THE PLEURAL CAVITY

The effect of injections of gum arabic broth on the cell counts of the exudate and the corresponding absence or occurrence of protection have already been presented. The precise degree of protection afforded three days after injection as compared with that given by aleuronat in the same period has not been determined accurately, although it will appear in subsequent discussion that sterilization is more rapid in the seventy-two hour aleuronat animal than in the corresponding gum arabic animal.



Fig. 4 (Rabbit 3104).—Parietal pleura seventy-two hours after injection of gum arabic broth into pleural cavity. Dense masses of rather flattened mononuclears (histiocytes and fibroblasts) extending down among muscle fibers. Few polymorphonuclears left; distinctly increased resistance against streptococcus. Average width, 155 microns; $\times 120$.

The total volume of the exudate in the aleuronat animal is one sixth of the amount of the gum arabic animal at the same period and would seem to account for the difference in result.

The pleura of animals killed eighteen hours after the injection of gum arabic is distinctly thicker than at the corresponding period in the aleuronat animals. The single animal examined at this period showed an average thickness of 133 microns. The pleura was edematous and contained for the most part polymorphonuclear cells, although not quite

as many as in the aleuronat animals. In addition more mononuclear cells were present.

By the third day the pleura had increased to six times its original thickness (average of 166 microns in four animals; fig. 4). The layer was filled with closely packed mononuclear cells which extended down in nodular masses among the muscle fibers. They represented an enormous increase in number. These cells varied in shape from ovoid to fibroblastic from one animal to another, and from place to place in the same animal. Blood vessels on the level of the superficial muscle fibers were prominent. The serosal cells were usually in good condition and continuous, but might be swollen.

In all instances when sections of the diaphragm were studied the changes were similar, with a large increase of mononuclears less regularly arranged but even more vascular.

TABLE 6.—*The Study of Exudates from a Series of Rabbits Prepared Seventy-Two Hours Previously with Gum Arabic Broth and Then Receiving Injections of a Large Dose of Stock Streptococcus (125 to 1,800 Million)*

Rabbit No.	Interval after Injection	Total Clasmato-cytes in Pleura in Millions	Total Poly-morpho-nuclears in Millions	Cultures, Per-centage	Phago-cyte Clasmato-cytes, Per-centage	Phago-cyte Poly-morpho-nuclears, Per-centage	Bacteria in Cells, Per-centage	Extra-cellular Bacteria, Per-centage	Bacteria Unac-counted For, Per-centage
Control average...		120	32
2028	12 min.	99	32	0.4	78	14	14.4	0.3	85.3
2022	30 min.	13½	2½	0.11	41	0	3.9	0.3	95.8
2024	135 min.	21	389	0.0018	37	0	8.8	0.6	90.6
2261	360 min.	240	912	0.0013
2032	23 hr.	151	567	Sterile	25	0	39.0	0.0	61.0

The serosa of the lungs also showed definite accumulation of mononuclears. Blood pigment was present both inside and outside these cells. Polymorphonuclears remained in larger numbers than in the parietal pleura.

When large numbers of stock streptococci were injected into the cavity prepared seventy-two hours previously with gum arabic broth, the following changes were noted in the exudate (table 6).

The total number of cells diminished at the thirty minute period and then steadily increased up through twenty-four hours, at which point they reached a total of approximately five times the number present at the time of injection. At the thirty minute period the decrease was equally evident on the part of both types of cells. At two and one-half hours the polymorphonuclears had increased to ten times the original number, and the mononuclears were still much fewer than at the time of injection. In six and twenty-four hours the clasmato-cytes had surpassed the original number and the polymorphonuclears were still further increased. The number of viable streptococci was decreased markedly

in thirty minutes to 0.1 per cent of their original number and continued to the point of sterilization in twenty-three hours. During the entire period phagocytosis was confined largely to the clasmatocytes. The initial proportion of clasmatocytes to polymorphonuclears at that time was as 4:1, but five times as high a percentage of clasmatocytes were phagocytic in twelve minutes, and later stages showed no polymorphonuclear phagocytes in spite of their great increase. In twelve minutes, 85 per cent of the bacteria as estimated from smears had disappeared, and in thirty minutes 96 per cent. To judge from cultures, less than

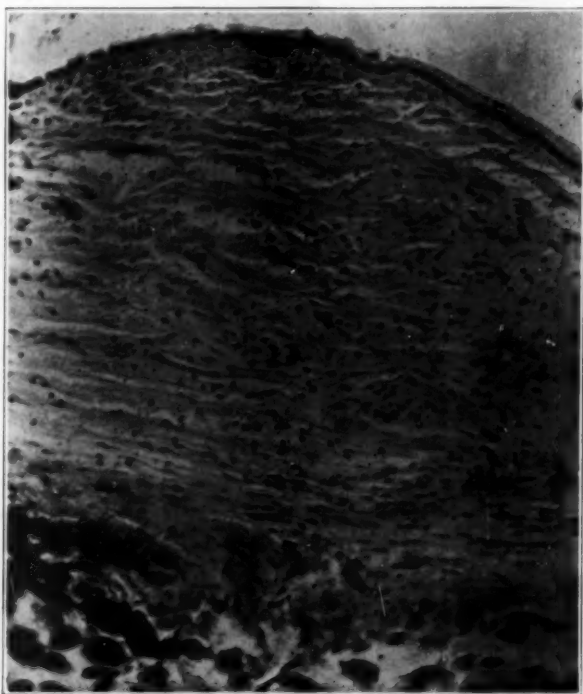


Fig. 5 (Rabbit 2042).—Parietal pleura of rabbit given one injection of gum arabic broth, followed three days later by stock streptococcus; then at week intervals two injections of passage streptococcus. Enormously thickened layer of granulation tissue, which averages 1107 microns. Tissue is rather loose, contains new blood vessels and in places accumulations of polymorphonuclear cells, as the animal was killed two hours after injection of a huge dose of stock streptococcus. (Bacteria can be found in clasmatocytes under an intact serosa.) Serosal cells have assumed cuboidal shape, owing to marked increase in number and consequent crowding; $\times 120$.

0.03 per cent of the bacteria visible in the cells were alive and 8 per cent of the bacteria outside the cells.

The histologic changes noted were as follows: In the twelve minute animal there was a notable mitosis on the part of the serosal cells and

mononuclears subjacent. As early as one-half hour after injection, polymorphonuclears appeared in the lower layers of the granulation tissue and increased in number at the two hour period. Phagocytosis of bacteria by mononuclears was also evident in this tissue. At twenty-four hours, there was still evidence of mitosis in the tissue, and enormous macrophages were present which contained polymorphonuclear cells.

The injection of small amounts of passage culture streptococci in a series of seventy-two hour broth animals showed the following changes (table 7): In half an hour the cells of both types were slightly reduced in the exudate. In two and six hours there was an increase in polymorphonuclears and a restoration of clasmatoocytes to their original numbers, apparently followed by a regression in twenty-four hours. The cultures, although sterile at the time of the first cell increase, rapidly increased up through the first day and then decreased to the point of sterilization on the third day. Phagocytosis was not marked in any of

TABLE 7.—*Study of Exudates from a Series of Rabbits Given a Small Dose of Passage Streptococcus "H" (3,000 to 3,750) Seventy-Two Hours After Injection of Gum Arabic Broth*

Rabbit No.	Interval after Injection	Total Clasmato- cytes in Pleura in Millions	Total Poly- morpho- nuclears in Millions	Cultures	Phago- cytic Clasmato- cytes, Percentage	Phagocytic Poly- morpho- nuclears, Percentage	Bacteria in Cells	Extra- cellular Bacteria
Control average....		120	32
3104	30 min.	98	30½	3.2%	0.2	×40	0
3109	120 min.	113	106	Sterile	0	0	0	0
3101	360 min.	112	210	×10½	0	0	0	0
3102	24 hr.	20	80	×78	0.4	0	×21	0
3110	48 hr.	3%
3111	72 hr.	Sterile

the intervals studied, owing to the small number of bacteria, and none were observed outside the cells at any time.

Histologically, the following changes were evident in the pleural cavity: In one-half hour there was a great distention of newly formed blood vessels, with some hemorrhage. The serosal cells were swollen, which condition continued during the two hour period. At six hours a few polymorphonuclears were evident; the serosa seemed intact and not much swollen, with slight hemorrhage. In animals killed two and three days subsequent to injection, at which time cultures from the pleura were sterile, the polymorphonuclears were present in the earlier animal but had disappeared in the three day animal, and there was evidence of further increase in the mononuclears which extended down in large masses among the muscle fibers.

The evidence so far presented deals with the condition of increased resistance to the streptococcus produced by injecting either one of two materials into the pleural cavity. These materials produce almost identi-

cal changes in the parietal pleura, which progresses through a stage of acute inflammation and polymorphonuclear infiltration to a condition resembling granulation tissue by the third day. These changes in the tissue are reflected by the relative proportion of polymorphonuclear cells and clasmatoctes in the pleural exudate, although the total number of cells present varies with the material employed and the amount of exudate produced in consequence. When the exudate is largely polymorphonuclear, that is to say, in the first day stage of animals inoculated either with gum arabic broth or aleuronat, there is a progressive increase in the number of virulent bacteria injected into the cavity (table 3), and correspondingly a progressive infection of the pleura as evidenced by extending necrosis.

When the exudate contains a proportionately large number of clasmatoctes, at least 100 times the dose of passage culture that is fatal to the animal in a condition of acute inflammatory exudate is harmless. The fate of such virulent organisms in small numbers differs in accordance with the amount of exudate that remains at the three day period, and that in turn depends on the material used in preparation. At this period the histology of the parietal pleura is similar in both instances. With a small amount of exudate and actually a smaller number of cells (table 4) sterilization of the cavity is rapid (two hours), whereas in the animal with a larger amount of exudate sterilization is not accomplished until the end of the third day (table 7). When virulent passage cultures in large and fatal amounts are employed, a more intimate picture of the phenomenon of phagocytosis and the destruction of bacteria as it goes on in the cavity is available (table 5). By employing a large amount of nonpathogenic stock culture (table 6), the behaviour of the chronic exudate can be contrasted with that of an acute inflammatory exudate (eighteen hour aleuronat starch animal, table 2). This comparison shows that sterilization of the harmless culture is more rapid and complete in the case of the chronic exudate; furthermore, evidence is clear that the majority of the bacteria introduced disappear from the cavity within a few minutes whereas their diminution in the acute inflammatory exudate is less pronounced. The comparison of the organisms found within and without cells in both instances as compared with cultures from the same exudates shows that a notable destruction of these organisms must have taken place in the cavity itself in a period of from twelve to thirty minutes. These results cannot be paralleled by any experiments we have devised outside the animal body with the same exudates. But even in the body it appears that the greater proportion of bacteria disappears rapidly and must be disposed of elsewhere. The mechanism of this destruction is evident in the histologic preparations which show phagocytosis by clasmatoctes in the subserous layer of the parietal pleura.

Throughout the whole process we have been discussing, phagocytosis, whether in exudate or tissue, is predominantly on the part of the clasmatoctytes, and the polymorphonuclears play little or no part in the process.

In brief summary, then, our present evidence corroborates the importance of mononuclear cells of the clasmatoctyte type in the local disposal of streptococci, but emphasis has now shifted, for reasons we have presented, to an apparent disposal of the bacteria by these cells in the tissues of the pleura rather than in the cell exudate itself. The exudate in origin and activity is simply a reflection of the conditions obtaining in the pleura.

Although our previous studies had led to an unequivocal demonstration that the mononuclear cells in the pleural cavity under the conditions of resistance and immunity are clasmatoctytes in the modern sense, as shown by supravital staining (neutral red), it remained to demonstrate that the same cells are present and active in the adjacent parietal pleura under the conditions of our present experimentation. This could readily be shown by injecting trypan blue directly into the pleural cavity, usually in a dosage of 2 cc. amounts, in two doses twenty-four hours apart, and by preserving the tissue in the usual manner in Zenker's fluid without acetic acid on killing the animal two days later (fig. 6). Intraperitoneal or intravenous injection of large amounts daily for a week or ten days stained fewer cells in any particular place, and moreover failed to give the evidence on pleural drainage to which we have referred. The characteristic cells which compose a considerable proportion, though by no means all, of the cells lying in the granulation tissue of the chronic inflammatory process, are found to contain large numbers of vacuoles filled with trypan blue. The sections may be dehydrated and counterstained in the usual fashion.

SPECIFIC LOCAL STREPTOCOCCUS IMMUNIZATION

Our remarks hitherto have dealt entirely with the matter of increased resistance to the streptococcus produced in the pleural cavity by non-specific agents. It remains to discuss the condition of specific active immunity produced by the injection of cultures of streptococcus. The method of preparing the cavity with broth or aleuronat facilitates specific immunization, since it is apparent that even a virulent passage culture may be injected without danger at a suitable chronic stage after the production of the sterile inflammation. Animals have been given from one to five injections subsequent to the treatment with broth or aleuronat in the same or in increasing amounts and with both stock and passage cultures. They recovered completely from such repeated injections in almost every instance, and on killing them subsequently in a

week or so following the last injection, they exhibited changes in the parietal pleura in particular which were simply an intensification of the process already described as produced by single injections of the non-specific sterile agent. Various degrees of increased thickening of the pleura, which may be as much as forty times the original, have been obtained in this fashion (fig. 5). One of the disadvantages in this method of immunization, although the animal may recover perfectly, is the frequent injury to adjacent tissues and localized areas of infection that remain in the chest wall or in the form of adhesions between the lung and the pleura. It is also difficult to enter the pleural cavity repeatedly with living bacteria without injuring the lung to a greater or less extent.

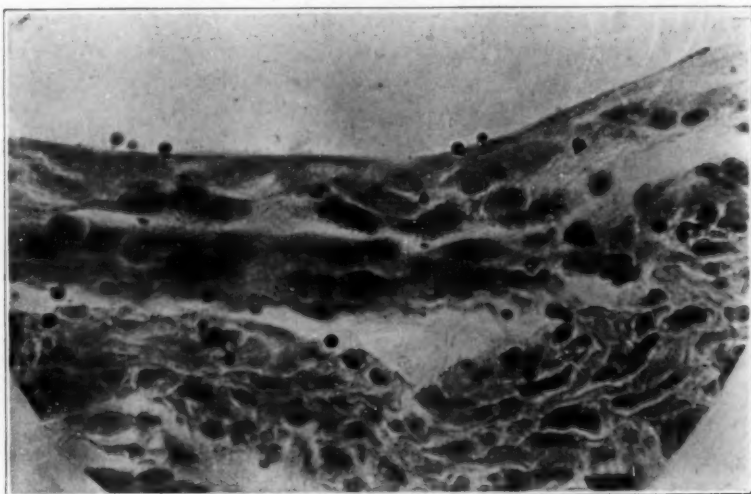


Fig. 6 (Rabbit 2055).—Parietal pleura of specifically immunized rabbit given an injection of 1 per cent trypan blue into pleural cavity two days before being bled. Clasmatocytes are seen under intact serosa selectively filled with masses of the dye; $\times 580$.

Although the culture from such cavities may be sterile, the relations between the pleura and adhesions to it to some extent confuse the picture and moreover render the location of a final dose, designed to test the protection of the animal, somewhat uncertain. We are now trying to obviate this difficulty by the use of killed cultures. At all events, we can assert that the degree of protection acquired by the repeated administration of living streptococci subsequent to broth or aleuronat preparation of the cavity is markedly increased over the protection obtained by a single injection of the broth or aleuronat. So far as we have gone, it appears that the degree of protection varies directly with the thickness of the granulation tissue that has been produced as measured in the parietal pleura.

These observations immediately raise the question as to the relation of increased resistance to specific immunization in a localized area, and particularly of the precise function of the cells in the thickened pleural wall in a nonspecific as contrasted with a specific condition. We have already said that there is an apparent quantitative relation of the number of cells to the degree of protection, but one cannot assume that the increased number of clasmotocytes alone explains the difference between increased resistance and the superior specific immunity. To answer this question, we have attempted to compare the degree of protection acquired by repeated injections of gum arabic broth as contrasted by the same number of injections of streptococci or some other micro-organism. It should be stated here that preliminary experiments indicated that several injections of *Staphylococcus aureus* will produce a tissue change in the pleura similar to that produced by the streptococcus, whereas the single animal that we have injected with the typhoid bacillus showed no histologic change except swelling of the serosal cells.

Experiment 1.—A group of adult rabbits was divided into three lots and treated as follows:

Lot A.: Eight rabbits. Three injections of 3 cc. each of gum arabic broth, spaced over a period of two weeks.

Lot B.: Eight rabbits. Three injections of 1 cc. stock "H" streptococcus, 1 cc. of diluted passage "H," and 1 cc. stock streptococcus in two weeks. One animal died of streptococcus pleurisy during immunization.

Lot C: Eight rabbits. Given three injections of *Staphylococcus aureus* (0.5; 1 cc.; 1 cc., twenty-four hour broth culture) in two weeks.

Six days after the last injection representatives of each series were killed for study of the treated cavities. In the case of the broth and staphylococcus series, additional controls treated on the third and fourth days with trypan blue were added.

Controls:

A. 2085: Given trypan blue. Cavity normal in appearance. Trace of fluid. Polymorphonuclears, 64 per cent. Histologically: Pleural wall thickened to average of 365 microns and filled with a preponderance of very large vacuolated cells containing trypan blue but not in as concentrated a form as usual. A few polymorphonuclear cells visible. Serosal cells swollen but continuity unbroken.

A. 2092: Normal cavity. Slightly thickened pleura (60 microns). Nodules of mononuclear cells.

B. 2084: Animal in poor condition. Cavity obliterated by loose adhesions and small abscesses. Fluid 20 cc. with many streptococci. Histologically: A necrotic exudate with debris of cells is found on top of a firm granulation tissue which extends down among muscle bundles. This tissue contains no polymorphonuclears.

C. 2087: Given trypan blue. Abscess about point of inoculation. Lung bound to pleura except at base. Trace of fluid. Small abscess in cavity gives cultures of staphylococcus. Histologically the parietal pleura is clear of adhesions in places. Characteristic trypan blue clasmotocytes in a thick layer of connective tissue (890 microns). Lymphocytes are more evident in the adhesions. No polymorphonuclears seen.

C. 2079: Adhesions to middle lobe of lung. Pleura less thickened (151 microns) with moderate number of mononuclear cells.

The remaining animals were subdivided into lots comprising two representatives from each series which were given the same dose of passage culture as follows, and with the resultant death or recovery noted:

Series 1: Given 1 cc. of 1:16,000 dilution passage streptococcus "H" containing 7,000 organisms = M. L. D. 50 (see controls).

2076 Gum arabic treated; recovered.

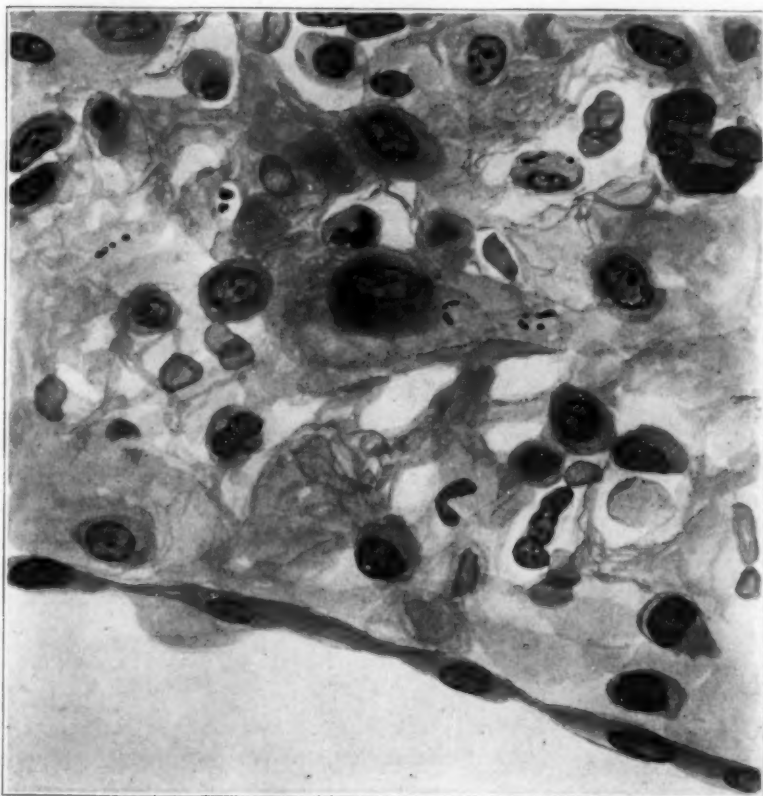


Fig. 7 (Rabbit 2042).—Parietal pleura from immune rabbit (see fig. 5) killed two hours after injecting 1 cc. of broth culture of stock streptococcus into cavity. This drawing, under oil immersion, is from a different spot than that chosen in fig. 5 and shows normal serosal cell layer with subjacent clasmatocytes that have caused phagocytosis of both bacteria and polymorphonuclear cells. It has estimated by culture and cell counts that only 2 per cent of the injected bacteria remained in the pleural cavity, of which one-half were dead.

2078 Gum arabic treated; dead 8 days; streptococcus pleurisy.

2080 Streptococcus treated; recovered.

2089 Streptococcus treated; dead 7 days; streptococcus pleurisy.

2088 Staphylococcus treated; dead 13 days; contaminating organisms.

2094 Staphylococcus treated; recovered.

Series 2: Given 1 cc. of a 1:1,600 dilution passage streptococcus "H" containing 70,000 organisms 500 M. L. D.

2073 Gum arabic treated; recovered.

2075 Gum arabic treated; recovered.

2085 Streptococcus treated; recovered.

2098 Streptococcus treated; dead 4 days; streptococcus pleurisy.

2090 Staphylococcus treated; dead 5 days; streptococcus pleurisy.

2086 Staphylococcus treated; dead 11 days; streptococcus pleurisy.

Series 3: Given 1 cc. of a 1:80 dilution passage streptococcus "H" containing 1,400,000 organisms = 10,000 M. L. D.

2071 Gum arabic treated; recovered.

2072 Gum arabic treated; dead 10 days; streptococcus pleurisy.

2082 Streptococcus treated; dead 4 days; streptococcus pleurisy.

2083 Streptococcus treated; dead 4 days; streptococcus pleurisy.

2100 Staphylococcus treated; dead 11 days; combined streptococcus and staphylococcus pleurisy.

2099 Staphylococcus treated; dead 9 days; combined streptococcus and staphylococcus pleurisy.

Controls: 2069 1 cc. dil. streptococcus "H;" passage 1:80,000 = 1,400 organisms; dead 5 days; streptococcus pleurisy.

2077 1 cc. dil. streptococcus "H;" passage 1:800,000 = 140 organisms; dead 3 days; streptococcus pleurisy.

3120 1 cc. dil. streptococcus "H;" passage 1:8,000,000 = 14 organisms; recovered.

3116 1 cc. dil. streptococcus "H;" passage 1:80,000,000 = 1+ organism; recovered.

This preliminary experiment would not indicate any superior and specific protection in the streptococcus immunized animals over that produced by repeated gum arabic broth. The treatment with streptococcus was apparently superior to that produced by staphylococcus. Any final decision in this important matter must depend on further experience under perfected conditions.

Another question of extreme interest is the relation of local immunity to general immunity in connection with an organism like the streptococcus. We have repeatedly presented our evidence for the existence of a condition of local immunity in streptococcus infections under experimental conditions and have shown that, although it is relatively simple to produce clear-cut immunity locally, it remains difficult and hazardous to produce strong generalized immunity. The same statement can probably be made as regards human immunity to streptococcus infection. The almost generally accepted futility of a true antibacterial serum therapy against streptococcus infections is further evidence of the lack of a general streptococcus immunity. If we admit that the local disposal of streptococci in a limited protected area is due entirely to the increase of clasmatoocytes in such an area, we can readily explain the superiority of strictly local as against general streptococcus immunity, but it is still

difficult to explain the condition of a more generalized but still somewhat localized skin immunity produced by experimental erysipelas in a limited area (Gay and Rhodes⁷). An experiment designed to throw light on this question follows.

Experiment 2.—Crossed pleural cavity immunity.

Adult rabbits 2050 and 2054 were immunized by injections into the right pleural cavity of 5 cc. of gum arabic broth followed three days later by 1 cc. of a twenty-four hour broth culture of stock streptococcus "H;" ten days later \pm 150 M. L. D. of passage streptococcus were given; seventeen and twenty-eight

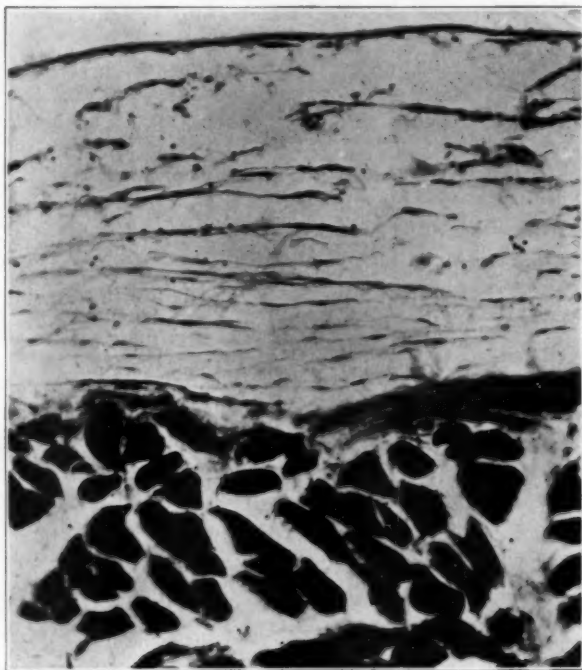


Fig. 8 (Rabbit 2054).—Right parietal pleura of rabbit immunized by injection of gum arabic broth followed by three injections of streptococcus and infected eight days later in left pleural cavity with 600,000 M. L. D. Killed three days later. Myxomatous granulation tissue (191 microns) stripped of its cells; \times 120.

days subsequently \pm 60,000 M. L. D. were given. Eight days later the animals were infected as follows:

Rabbit 2050 was given \pm 600,000 M. L. D.* (0.1 cc. of twenty-four hour broth culture) into right pleural cavity. Rabbit killed by bleeding three days later, with the following findings:

7. Gay and Rhodes: J. Infect. Dis. **31**:101-115, 1922.

8. This multiple is estimated from exact determinations made over one year previously and may have altered slightly, but certainly not more than by a multiple of ten (exper. 1).

Right Pleura: No muscular abscess in wall. Pleural cavity filled with granulation tissue and dense adhesions which united parietal pleura with lung over its entire surface; lung otherwise appeared normal. Cultures from pleural cavity sterile.

Histology: Enormously thickened pleura but difficult to measure owing to continuation of granulation tissue between serosa, which was not clearly defined, and lung. The tissue consisted of round and elongated mononuclear cells (clasmatocytes and fibroblasts). Areas of lymphoid cells scattered throughout. Few polymorphonuclears seen. New blood vessels. Large round mononuclear cells were enveloping red blood cells and polymorphonuclears.

Left Pleura: Parietal pleura and lung were normal in the gross and histologically. Blood cultures sterile.

Rabbit 2054 was given \pm 600,000 M. L. D. into *left* pleural cavity. Killed three days later.

Right Pleural Cavity: Old adhesions between upper lobe of lung and parietal pleura contained small walled off abscess. Culture sterile. No fluid in cavity; 1 cc. of broth introduced and gave sterile culture. Intercostal muscles and lung were normal.

Histologic: Parietal pleura in places was of nearly normal thickness. In other places it measured on the average 191 microns ($\times 7$). The tissue was loose (myxomatous) and contained much fewer cells than the average in this condition (fig. 8). (Suggests that cells had been stripped from this area for mobilization to other pleura?)

Left Pleural Cavity: Contained 2 cc. blood stained fluid. *Cultures sterile.* Evidence of an acute serofibrinous pleurisy which, however, was wholly unlike the normal fatal pleurisy on the third day, at which time the exudate averages from 8 to 10 cc. and contains enormous numbers of streptococci and only the debris of cells. It was also unlike the result of injection into an immunized pleura which at this period contained no fluid. Polymorphonuclears, 37 per cent; clasmatocytes, 43 per cent, and many granules (bacteria?); lymphocytes, 20 per cent; no extracellular bacteria.

Histology: Parietal pleura. Thickened pleura with serosa irregular, swollen and broken. Mononuclears and polymorphonuclears infiltrated the thickened layer which measured 90 microns.

A very unusual distribution of mononuclear cells was evident (fig. 9), which infiltrated the muscle bundles to a great depth in nodules and strands. Polymorphonuclears were interspersed.

This experiment was corroborated, though to a less conclusive degree, by an infection of the opposite pleural cavity in the animal that had been simply protected by means of gum arabic broth. Such experiments seem to indicate that not only may the increased cells in a pleural cavity, or more particularly in the parietal pleura adjacent to such a cavity, protect the local area, but also that these or other cells produced as a result of this sterile inflammation may be mobilized at another point in the body and produce similar results. This experiment, moreover, throws light on a question that may naturally arise as to the importance of the clasmatocytes themselves in the modified parietal pleura. The entire protective effect might be due to a mechanical barrier produced by the granulation tissue rather than to any intrinsic destructive properties of the cells

themselves. These cross infection experiments would seem to show that it is the cells rather than the preexisting barrier that produce the results obtained.

SUMMARY AND CONCLUSIONS

This article describes first the histologic changes that take place in the pleura of rabbits as the result of the injection of sterile aleuronat or gum arabic broth mixtures. These changes are earlier and more marked in the parietal pleura and diaphragm, through which drainage of the pleural cavity takes place, than in the visceral (lung) covering. The

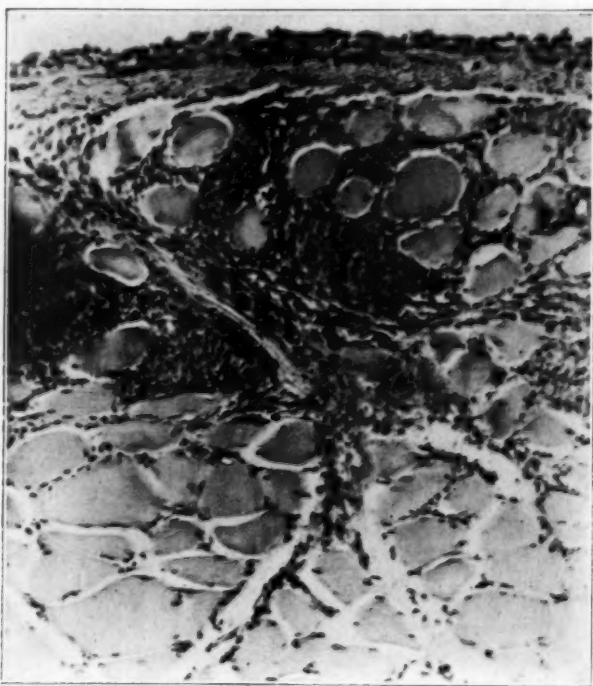


Fig. 9 (Rabbit 2054).—Left parietal pleura of rabbit immunized on right side and injected left side. Killed three days later. Thickened pleura (90 microns) with unusual infiltration of clasmatocytes in muscle bundles. Mobilization of cells; $\times 120$.

changes are similar with the two substances employed, and, owing to the delicacy of the tissue involved, show remarkable differences from normal in the nature of an acute inflammation followed by a more chronic condition in the nature of granulation tissue. Infiltration with polymorphonuclear cells on the first day is replaced by an intensified thickening due to mononuclear cells by the third day. By vital staining with trypan blue a preponderating number of these mononuclear cells are shown to be true clasmatocytes or tissue macrophages.

We have previously discussed the cytology of the pleural exudate which we now find to be a reflection of the tissue changes here emphasized. We had shown that there is a definite relation between the cell picture and presence or absence of an increased resistance to infection with a strain of *Streptococcus pyogenes* that produces in minute doses a fatal pleurisy. The correlation indicated that the clasmatoocytes are responsible for protection. This correlation is further emphasized by the tissue changes we have now described. An acute inflammatory pleura is invaded and destroyed by virulent streptococci injected into the pleural cavity, whereas the same organisms disappear rapidly from the pleural cavity of animals with granulating and thickened pleural walls and are found enveloped within clasmatoocytes in a relatively undisturbed tissue. Phagocytosis of streptococci both in the exudate and tissues is almost exclusively by mononuclear cells.

The pleural wall may be thickened still further by repeating the injection of the nonspecific substances or by injecting living streptococci. The degree of protection would seem roughly commensurate with the depth of granulation tissue that has been produced. We are unable as yet to say whether specific immunity produced by the streptococcus differs from increased resistance produced by nonspecific and sterile irritating agents in possessing some specific factor; in other words, whether all grades of local streptococcus protection are dependent simply on the number of clasmatoocytes present.

Preliminary experiments show that when one pleural cavity is treated sufficiently, the other cavity, although showing no histologic change in the pleural wall at the time of infection, is nevertheless protected. This protection is accompanied by mobilization of clasmatoocytes in the pleural wall in an unusual fashion; there is further indication that the wall of the treated cavity is coincidentally stripped of its cells.

HISTOLOGIC CHANGES FOLLOWING ADMINISTRATION OF IODINE IN EXOPHTHALMIC GOITER *

ALFRED S. GIORDANO, M.Sc., M.D.**
SOUTH BEND, IND.

That iodine produces a marked remission of the clinical symptoms in exophthalmic goiter as originally reported by Plummer in 1923,¹ is now generally accepted by clinicians. With this in view, an attempt was made to correlate the histologic changes found in hypertrophic parenchymatous thyroid glands following iodine therapy with the clinical course of the disease. In a preliminary report,² I stated that the involution changes occurring after the ligation of the thyroid vessels in exophthalmic goiter were also present in the glands of patients who had received iodine previous to thyroidectomy. Rienoff,³ working independently, has published an excellent article on this subject corroborating my observations. In his study, he obtained a section of the gland before the administration of iodine as a basis of comparison. At this time, I wish to sum up my observations in a more detailed form.

This investigation was begun at the Mayo Clinic under the supervision of Dr. A. C. Broder and continued in my laboratory subsequent to 1923. The material selected consisted of a group of sixty-eight thyroid glands removed from patients with exophthalmic goiter who had received iodine before operation. The duration of the medication varied from one week to three months. Sections were taken from all poles of these glands, fixed in formalin, and sections cut by the fixed frozen or paraffin method.

In order to establish a basis for comparison, I have selected a group of thyroid glands taken at necropsy from exophthalmic goiter patients dying during crises. These glands, grossly, had a meaty appearance, and on section little or no colloid escaped from the cut surfaces. The microscopic picture was characterized by the presence of relatively small acini lined with high columnar epithelium. The lumina of the acini contained little or no colloid substance. There were numerous folds of paren-

* Read before the American Association of Pathologists and Bacteriologists, April 3, 1926.

** From the South Bend Medical Laboratory.

1. Plummer, H. S., and Boothby, W. M.: *J. Iowa State M. Soc.* **14**:66, 1924.

2. Giordano, A. S.: Iodine in the Treatment of Exophthalmic Goiter, *J. Indiana State M. Assn.* **19**:63-65, 1926.

3. Rienoff, W. T.: The Histologic Changes Brought About in Cases of Exophthalmic Goiter by the Administration of Iodine, *Bull. Johns Hopkins Hosp.* **37**:285-305, 1925.

chymatous cells projecting into the cavity of the acini. The lymphatic and the blood vessels were markedly distended (fig. 1).

With these facts in mind, we can then compare tentatively the histologic changes that take place following the administration of iodine. Grossly, these glands were pale, and the cut surfaces had a glossy gray color due to the large amount of colloid. The microscopic changes were characterized by markedly dilated acini filled with colloid, and a transition of the epithelial lining of the acini from high columnar to cuboid type (figs. 2 and 3). In many instances, the infolding processes noted in figures 1 and 2 were mostly ironed out or entirely absent. In places this

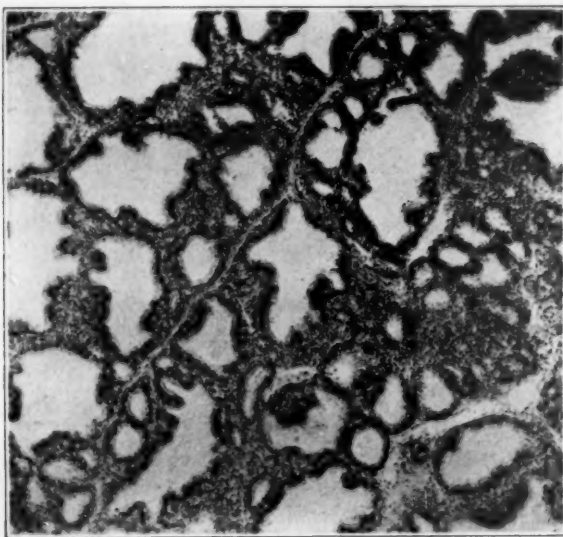


Fig. 1.—Control. Small acini lined by high columnar epithelium, with infolding processes in the lumina; $\times 90$.

infolding was represented by a simple frame work covered with low, cuboidal epithelium or none (fig. 4). The lumina of the acini were occasionally found to contain clumps of desquamated epithelial cells undergoing degeneration (fig. 5). An apparent increase of connective tissue was occasionally seen, but it is difficult to ascertain whether this is true fibrosis as described by Rienoff or simply a relative increase due to atrophy of the parenchyma. Lymphocytic infiltration was also frequently seen in many glands, but I believe it is of no significance, since it is frequently found in glands of untreated patients. Of the glands in which the preoperative administration of iodine was exceeded by a month or more and accompanied by a sharp clinical improvement of the symptoms, the involution changes were so marked that the diagnostic

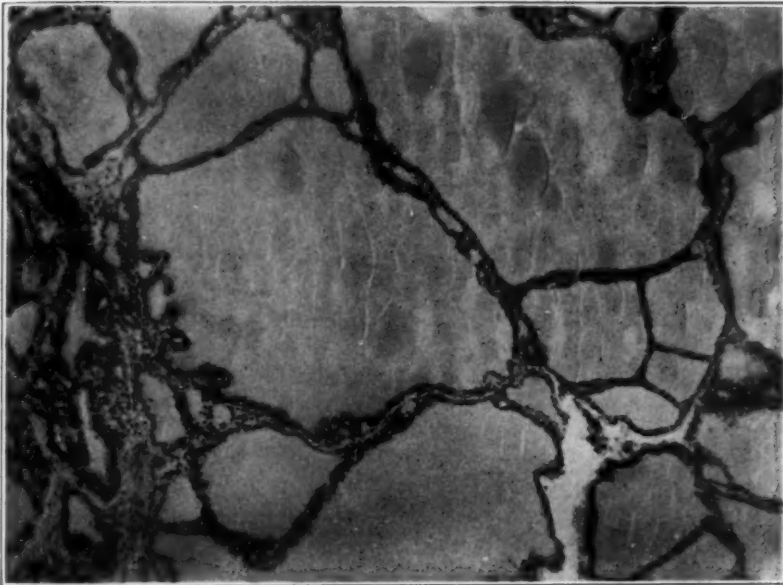


Fig. 2.—After administration of iodine. Dilatation of acini lined by a low columnar or cuboid epithelium and filled with colloid; $\times 100$.

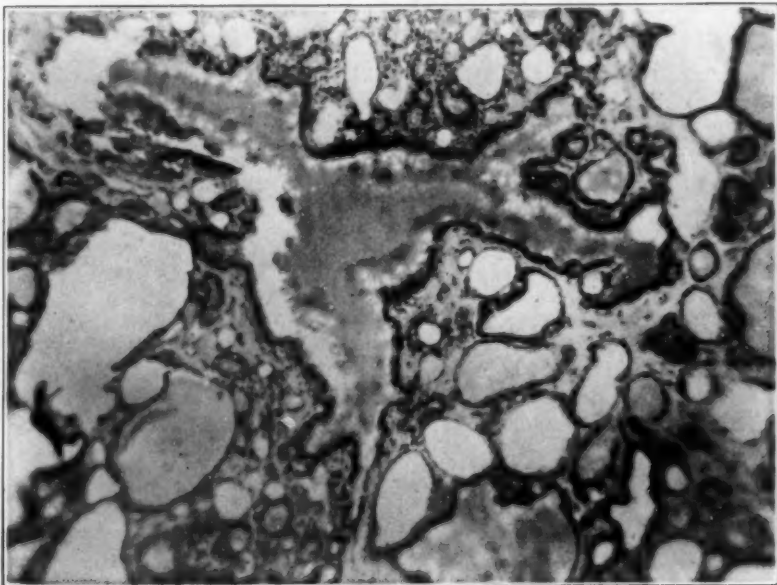


Fig. 3.—Single acinus lined with columnar epithelium while the remaining acini are lined with cuboid epithelium; $\times 100$.

evidences of exophthalmic goiter were difficult to ascertain histologically, and in many cases the only histologic suggestion that the gland was from a patient with exophthalmic goiter was the finding of acini containing sprigs projecting into their lumina or an occasional acinus lined by low columnar epithelium (fig. 4), assuming that formerly these sprigs represented the infolding processes already described.

On reviewing the clinical histories of these patients and comparing the histologic picture of the respective glands, it was at once apparent that the degree and extent of involution was closely paralleled by and corresponded to the clinical improvement of the symptoms, with a few exceptions. The following case reports will illustrate these points.

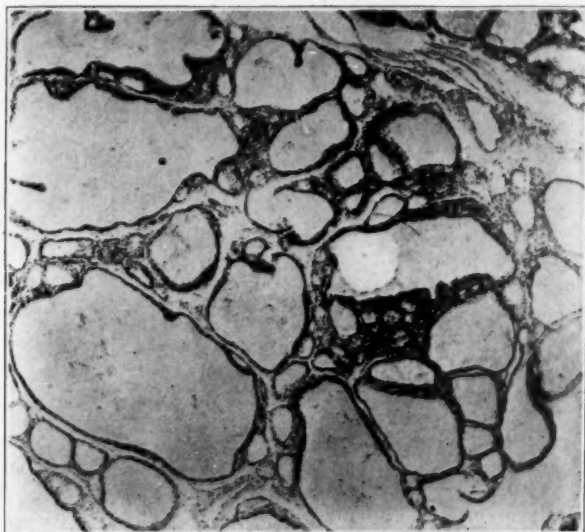


Fig. 4.—Sprig-like projections into acini representing remains of infolding of acini seen in figures 1 and 2; $\times 100$.

REPORT OF CASES

CASE 1.—Mrs. I. K., aged 26, complained chiefly of weakness, nervousness, loss of 15 pounds (6.8 Kg.) in weight during the past three months, profuse perspiration and enlarged thyroid. Examination revealed: exophthalmos 3+; bruit and thrills over the thyroid vessels; quadriceps weakness 2+; pulse rate 120 and the basal metabolic rate +97. The patient was given 3 cc. of Lugol's solution a day. During the following ten days, the pulse gradually fell to 90, and the basal metabolic rate was +35. The patient was subjectively improved. Partial thyroidectomy was performed at this time. The portion of the gland removed had a glossy appearance typical of colloid increase. Microscopic examination revealed the usual involution changes described, except that scattered throughout the sections there still remained areas of apparently active acini (fig. 3).

CASE 2.—Mr. T. L. L. was admitted to the hospital on March 23, 1923, with typical symptoms of exophthalmic goiter. The basal metabolic rate was $+53$ and the pulse rate was 110 per minute. Three cubic centimeters of Lugol's solution was given daily. The clinical symptoms began to improve, and on March 30, the basal metabolic rate was $+28$. On April 3, the basal metabolic rate was $+13$. The patient felt so well that he refused operation and returned home. He was readmitted on April 15, with a return of previous symptoms and a basal metabolic rate of $+61$. Lugol's solution was given again as above, and clinical improvement was apparent. On April 23, the basal metabolic rate was $+45$; on April 28, $+24$; on May 10, the basal metabolic rate was $+15$ and the pulse rate 78 a minute. The patient returned home with instructions to continue using 1 cc. of Lugol's solution daily. On June 5, the patient returned for thyroidectomy feeling perfectly well, with a basal metabolic rate of $+10$. The

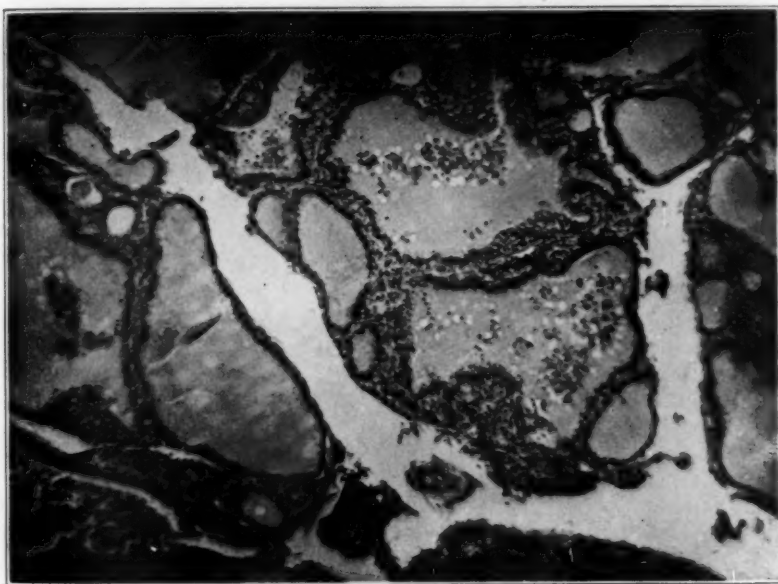


Fig. 5.—Epithelial desquamation; $\times 100$.

extirpated portion of the gland had the characteristic grayish shiny appearance. Microscopic examination revealed almost complete involution to a colloid goiter. The acini were lined by a low cuboid epithelium, and only rarely an occasional acinus was found lined by low columnar epithelium (figs. 6 and 8).

CASE 3.—Miss A. H. complained chiefly of nervousness, muscular weakness, palpitation, and loss in weight in spite of a ravenous appetite. The basal metabolic rate was $+68$ and the pulse rate was 118 per minute. Three cubic centimeters of Lugol's solution was given daily. After the third day subjective clinical improvement was noted. The basal metabolic rate was $+50$. Two weeks later the basal metabolic rate was $+15$. The patient returned home feeling entirely relieved of symptoms and having a pulse rate of 79 per minute. Three months later, the patient returned to the hospital with a recurrence of the previous symptoms following an attack of tonsillitis. The basal metabolic rate was $+62$ and the pulse rate 112 per minute. Three cubic centimeters of Lugol's

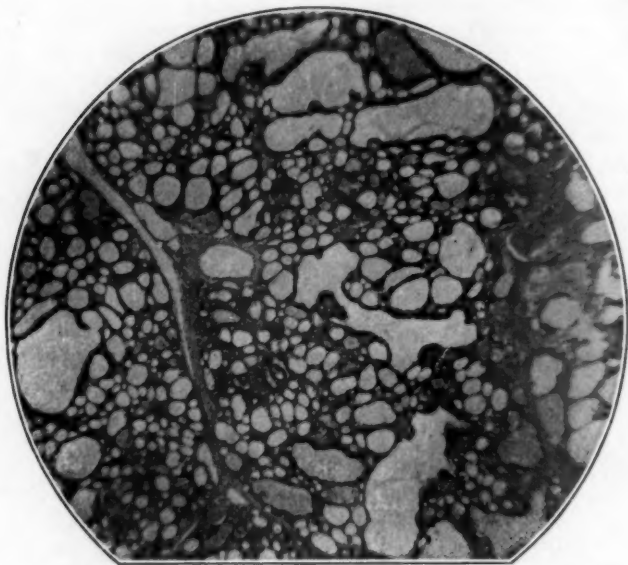


Fig. 6.—Marked involution to colloid type with only an occasional acinus lined by columnar epithelium; $\times 50$.

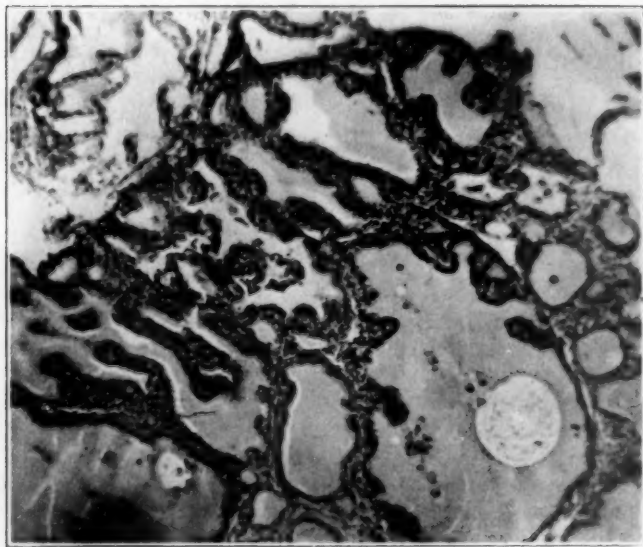


Fig. 7 (case 3).—Relatively active acini; $\times 100$.

solution was given daily. During the first week there was only slight improvement of subjective symptoms. Lugol's solution was increased to 5 cc. daily. The basal metabolic rate was +59. During the following three weeks, there was no appreciable clinical improvement. The basal metabolic rate was +50 and the pulse rate 90 a minute. Partial thyroidectomy was performed. Sections from the gland showed a relatively active gland with only moderate involution changes (fig. 7).

CASE 4.—Miss F. B., aged 28, complained chiefly of nervousness, palpitation, loss of weight and exophthalmos. The duration of the symptoms was four months. The pulse rate was 110 a minute and the basal metabolic rate was +76. Three cubic centimeters of Lugol's solution was given daily. During the following ten days the pulse varied from 96 to 104 a minute, and the basal metabolic rate was +47. The patient felt slightly improved. Lugol's solution was increased to 4 cc. daily, but with no further improvement during the next ten days. Thyroidectomy was performed. The extirpated gland had the characteristic appearance of colloid goiter. Microscopically, no recognizable evidence of

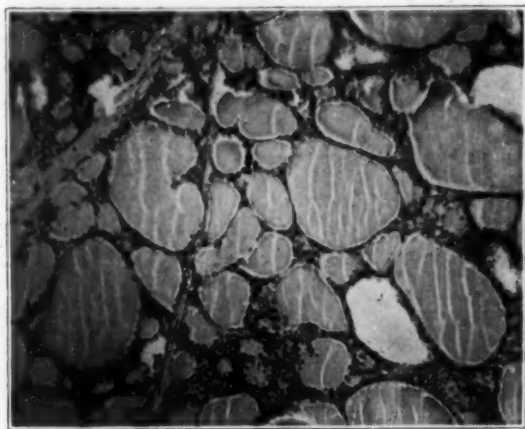


Fig. 8 (case 2).—Complete involution to colloid goiter; $\times 100$.

hypertrophy or hyperplasia could be found. The acini were dilated, filled with colloid and lined by low cuboid epithelium. When we compare the striking histologic findings to the relatively slight improvement of the symptoms, it is at once apparent that the anatomic and the clinical course do not always run parallel.

COMMENT

From the present study there was found evidence that in most instances involution changes in the thyroid gland occur when iodine is administered to patients with exophthalmic goiter, and that, in general, the degree of involution of the thyroid parenchyma closely parallels the clinical course. The changes are similar in character to those described following ligation of the thyroid vessels,⁴ but they occur rather uniformly

4. Giordano, A. S., and Caylor, H. D.: Histologic Study of the Effect of Ligation of the Thyroid Vessels in Exophthalmic Goiter, *Surg. Gynec. & Obst.* **36**: 75-80, 1923.

throughout the gland. It seems fair to assume that these changes are not characteristic of the method that induces them, for I have also observed them in patients who came to operation during a period of remission of the clinical symptoms without any therapy other than rest. On the other hand, we have yet to explain the occurrence of marked involution changes in patients with definitely active true ophthalmic goiter. Such an occurrence is admittedly rare, but as yet no definite explanation has been given. This suggests that the anatomic picture does not always parallel the clinical course.

SYMMETRICAL CORTICAL NECROSIS OF THE KIDNEYS IN PREGNANCY *

WILLIAM J. CARSON, M.D.

AND

REED ROCKWOOD, M.D.

BALTIMORE

Bradford and Lawrence in 1898¹ first described symmetrical cortical necrosis of the kidneys in pregnancy. Lloyd² and others have since reported single cases. Jardine and Teacher³ in 1910 reported two cases, and Jardine and Kennedy, in 1913,⁴ reported three cases, the latter being the only observers to study more than a single case. Rolleston, in 1913,⁵ in a complete review of the literature, was able to collect eleven cases found in pregnancy and one case following scarlet fever,⁶ adding one case of his own.

Glynn and Briggs reported a case in 1915⁷ with a most excellent description of the microscopic findings. Because of the rarity of the condition, we wish to add a case in which the gross and microscopic findings are nearly identical with those of Glynn's.

REPORT OF CASE

History.—Mrs. B. J., aged 36, sextipara, entered the University Hospital on Nov. 24, 1925, in the sixth month of pregnancy, with no symptoms until about one week before admission, when she began to complain of vomiting, nocturia and oliguria. On admission she was disoriented and irrational, with failing memory. She was dehydrated and was unable to retain any solid food and frequently vomited water.

Physical Examination.—The patient showed a blood pressure of 200 systolic and 130 diastolic, marked edema of the optic disks with cotton wool exudates and tortuous vessels with increased light streak. There was no general edema on admission.

The urine showed a specific gravity of 1.015, albumin 4 plus, many red and white cells and many hyaline and granular casts in a voided specimen. The non-protein nitrogen of the blood was normal at this time.

* From the Department of Pathology, University of Maryland.

1. Bradford, J. Rose, and Lawrence, T. W. P.: J. Path. & Bact. **5**:197, 1898.
2. Lloyd, Cairns: Lancet **1**:156, 1906. Griffith and Herringham: J. Path. & Bact. **11**:237, 1906. Klotz, Oskar: Am. J. Obst. **58**:619, 1908.
3. Jardine and Teacher: J. Path. & Bact. **15**:137, 1910.
4. Jardine and Kennedy: Lancet **1**:1291, 1913.
5. Rolleston, H. D.: Lancet **11**:1173, 1913.
6. Torrens, J. A.: Lancet **1**:99, 1911.
7. Glynn, E. E., and Briggs, H.: J. Path. & Bact. **19**:321, 1915.

About eight hours after admission, she was spontaneously delivered of a dead fetus more than 6 months old, which was so badly macerated that spontaneous decapitation occurred during labor. The blood pressure promptly dropped to 150 systolic and 100 diastolic and vomiting decreased. This temporary improvement continued for twenty-four hours, after which the patient became worse. The blood pressure rose to 170 systolic and 110 diastolic. She was completely anuric for twenty-four hours, and then passed a small amount of urine. Until her death on Nov. 30, 1925, there were no convulsions, although the patient was very drowsy. She died suddenly, apparently while asleep.

The clinical diagnosis was acute glomerular nephritis of pregnancy and cerebral edema.



Fig. 1.—Left kidney and posterior half of right kidney.

Necropsy (Dec. 1, 1925).—The capsules of the kidneys stripped off with marked resistance, leaving a finely granular lemon yellow surface, with a large number of small red areas due to dilated capillaries and small petechial hemorrhages. On section the whole cortex, including the columns of Bertini, was lemon yellow, in sharp contrast to the dark red medullary portion. The renal arteries showed no thrombi. A cyst was seen in the upper and lower pole of each kidney. The right pelvis was moderately dilated, and the mucosae of the pelvis and calices were dark reddish.

Microscopic Examination.—Sections taken from various parts of the kidneys showed the capsule to be moderately thickened due to adult connective tissue fibers, which were for the most part poorly stained. Just beneath the capsule,

there were tubular epithelial cells, which were poorly stained. The cell outlines were scarcely visible. In a few areas the capsules of Bowman and the tufts could be made out as such; the capsules were moderately thickened and their connective tissue cells were poorly stained. The epithelial cells lining the capsules of Bowman were fragmented and found free in the space, with leukocytes, a few red blood cells and other cells which could not be identified. The glomerular tufts showed the endothelial and epithelial cells poorly stained, with their arterioles filled with blood platelets. In most areas throughout the cortex, the tufts and tubules were poorly stained. There was a diffuse coagulation necrosis. Between the tubules there was a slight increase of adult connective tissue cells visible in the areas where the tufts could be identified. A large number of inter-

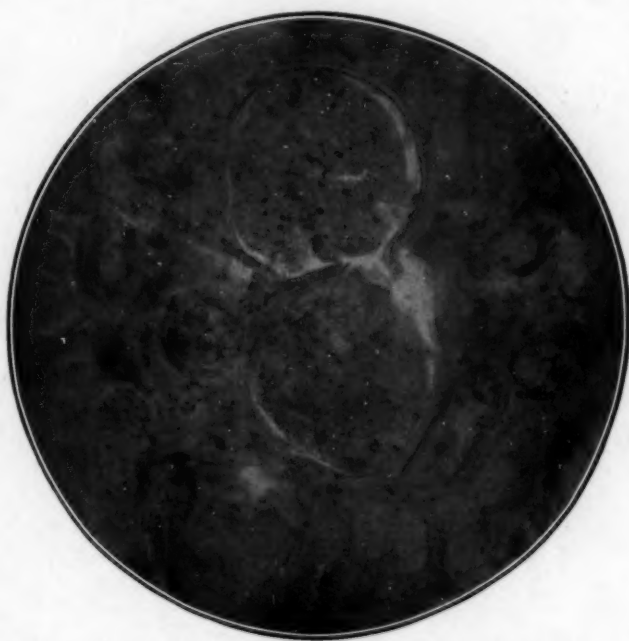


Fig. 2.—High power magnification of necrosis of two glomerular tufts and a number of tubules.

lobular arteries showed a definite destruction of their endothelium, with a layer of blood platelets adherent to the tunica media. Some of the arterioles were completely filled with platelets and a scant amount of fibrin. A few vessels showed the intima only partially destroyed.

In the corticomedullary zone, there was a moderate infiltration of leukocytes and mononuclear wandering cells. In the medullary portion, the tubular epithelial cells were fairly well preserved, with a slight increase of connective tissue between the tubules.

Anatomic Diagnosis.—Retained placenta; hypertrophy of the uterine wall; hydroureter; hydronephrosis, right; cystitis; ureteritis, bilateral; pyelitis, bilateral; chronic diffuse nephritis; acute glomerular nephritis with symmetrical cortical necrosis of the kidneys in pregnancy; thickening of the mitral valve, moderate; hypertrophy of the left side of the heart, moderate; terminal hypostatic congestion of the lungs; edema of the brain and ankles.

COMMENT

Two clinical points are of interest in this group of cases. In the first place, a study of the literature shows only one case of a live birth, and it is to be noted that the child had long been dead in our case. In the second place, anuria appears to be a characteristic symptom, probably due to the intense cortical destruction. This fact should perhaps make us suspect the existence of this type of lesion in the future, since an anuria is not frequent in the ordinary toxemias of pregnancy.



Fig. 3.—High power magnification of thrombi of blood platelets, fibrin and a few leukocytes in a thickened interlobular artery.

Rockwood, Mussey and Keith,⁸ have recently called attention to the many similarities existing between the toxemias of pregnancy and the ordinary acute glomerular nephritis seen during the war and in civil life. This case also clearly shows the extensive glomerular damage, which was apparently the earliest evidence of renal pathology in this patient.

SUMMARY AND CONCLUSIONS

Typical symmetrical necrosis of the kidneys is apparently invariably associated with pregnancy. Fourteen cases have been recorded.

8. Rockwood, R.; Mussey, R. D., and Keith, N. M.: A Clinical Study of Nephritis in Cases of Pregnancy, *Surg. Gynec. & Obst.* 42:342, 1926.

The necrosis is due to thrombosis of the interlobular arteries, their afferent branches and glomerular capillaries.

It is our opinion that in cases of this type there is an acute glomerular nephritis with an injury to the vascular endothelium from a toxin circulating in the blood stream, followed by the formation of thrombi composed of blood platelets and fibrin.

MITOTIC FIGURES IN MALIGNANT TUMORS AS AFFECTED BY TIME BEFORE FIXATION OF TISSUES *

NEWTON EVANS, M.D.

LOMA LINDA, CALIF.

In the study of the histology of malignant tumors I have been led to regard the number of mitotic figures visible in tissue sections as an important factor in making a diagnosis of malignancy and in estimating degrees of malignancy in different tumors of a given type. Several years ago in making a comparative study of the clinical aspects of a large group of so-called malignant tumors of the body of the uterus—malignant myomas—as related to the microscopic findings in the tumors, I was impressed with the importance of the numbers of mitotic figures present in a given tumor as an indication of its malignancy.¹ In a group of seventy-five tumors which had previously been called malignant from a histologic standpoint, it was learned by comparing the histologic findings with the clinical aspects that only thirteen of these were tumors whose behavior was definitely malignant. In every such case the tumor tissue contained large numbers of mitotic figures. There was also a considerable portion of the entire group of tumors studied which contained mitotic figures easily detected and counted, but in much smaller numbers than in the thirteen cases mentioned; but none of these showed any malignant characteristics. The remainder of the group, a majority of all of them, contained practically no visible mitotic figures. The latter were also clinically nonmalignant, notwithstanding the fact that they had previously been diagnosed as malignant, such opinion being based on the general character of their cellular structure.

At that time it occurred to me that it might be helpful to make an actual numerical computation of the numbers of such figures present, and to express these figures in terms of their number in a cubic millimeter of tissue, in a manner analogous to the expression of the number of leukocytes per cubic millimeter of blood. Table 1 in that article gives an idea of the actual numbers of such cells in the tumors of the group studied, together with other facts of importance relating to these tumors.

We are familiar with the fact that in a general way the presence of numerous mitotic figures in tumor tissue is one of the characteristics of malignancy, but by some their real importance as a diagnostic factor is

* From the Department of Pathology, College of Medical Evangelists.

1. Evans, Newton: Malignant Myomata and Related Tumors of the Uterus, Surg. Gynec. Obst. **30**:225, 1920.

not emphasized. Dr. A. C. Broders of the Mayo Clinic in his notable work on the grading of epithelial tumors as to degrees of malignancy, lays special stress on two points in their histology. First, the comparative degrees of differentiation of the epithelial tissue present, and second, the relative frequency of mitotic figures in such tumors.

In view of the apparent importance of the presence of numerous mitotic figures in the diagnosis of malignancy, the question has presented itself as to the possibility of their numbers being materially modified by the manner in which tumor specimens are cared for after removal from the body. In fact, this question has been advanced by some as a criticism of the idea that the number of mitotic figures present in any tumor is of any importance on account of the fact that the number may be materially altered after the removal of the specimen. It is a fact that such pathologic specimens are often kept for hours at room temperature before being immersed in the fixing or preserving fluid.

It may be argued that if it is true, as has been conclusively shown, that the cell division process is ordinarily completed in a period of time varying from one-half hour to a very few hours at the most, then why should not one expect that those cells in a state of mitosis at the instant of removal of the tissue from the influence of the body circulation perhaps do complete the process and return to the resting stage, while other cells which otherwise might have entered on such a process remain quiescent? In fact, the following statement is made in Mallory and Wright's² "Pathological Technique," p. 104, "Mitotic figures can be demonstrated in tissues which have been dead for some time (twenty-four hours or more) before being put into a fixing reagent, but the details of the figures are not so perfect as those in absolutely fresh tissues and the figures are not so numerous, because some of them have completed their changes and can no longer be recognized."

With these considerations in mind, I planned an experiment to determine the effect on tumor tissue of being kept for varying periods of time in the unfixed state. At the present time, we have succeeded in making such observations on two tumors. Case 1 was a mixed cell sarcoma of the thigh, the cells of rather large size, of spindle, round and irregular shape. The mitotic figures were abundant. There were large areas of necrosis. Case 2 was also a sarcoma of typical spindle shaped cells of comparatively small size. The numbers of mitotic figures present were comparatively small.

The details are as follows: Of each of the tumors, three portions of suitable size were selected. Of these one was kept at room temperature, one in the icebox and one in the incubator at body temperature. At

2. Mallory and Wright: Pathological Technique, ed. 8, Philadelphia, W. B. Saunders Company, 1924.

stated intervals fragments of each of these, of suitable size for the preparation of sections, were dropped into 10 per cent formaldehyde solution for fixing. These periods were immediately after removal from the body, one-half hour, one hour, one and a half hours, two hours, three hours, four hours, five hours, six hours, etc., up to twenty-four hours. All of these fragments later were sectioned and stained with hematoxylin and eosin, and by examination under the oil immersion lens the number of figures in approximately 100 fields were counted.

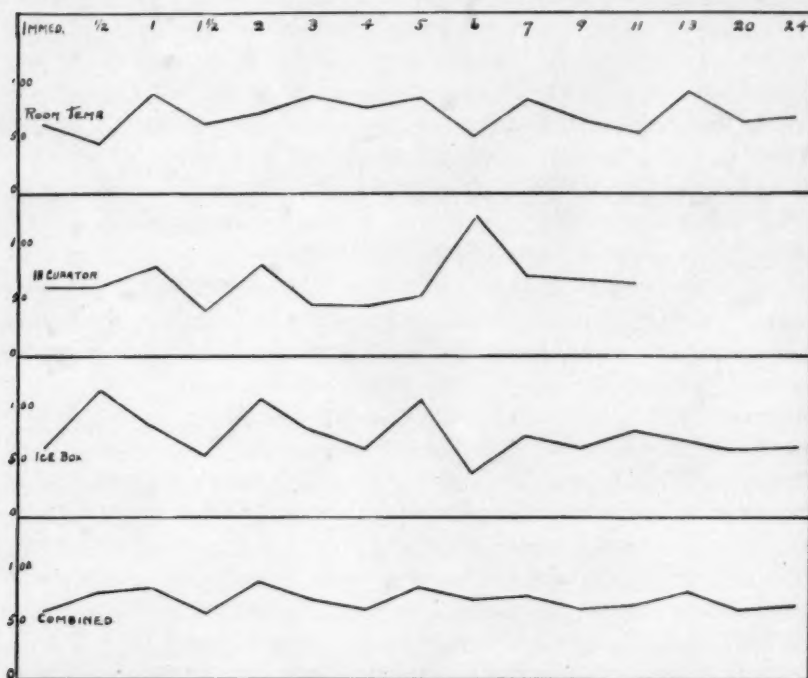


Chart 1 (case 1).—Mitotic figures seen in 100 oil immersion fields in fragments kept at room temperature in incubator and icebox, respectively. The ordinates represent the number of mitotic figures; the abscissas, the length of time in hours each fragment was kept after removal before fixation.

The results of these observations are shown in the graphs herewith presented. Chart 1 (case 1) shows the number of mitotic figures seen in 100 oil immersion fields in the fragments kept for varying periods before fixation, at room temperature, in the incubator and in the icebox, respectively. It also includes a tracing in which these three are combined showing the average of the counts for each time period.

Chart 2 presents similar observations in case 2.

One will note the rather wide variation in the counts on different sections. It is evident that these are due to the unevenness of the tumor

tissue in its different portions and not to actual changes due to treatment of the fragments. This accidental variation is in some degree corrected by combining the counts of the three sections representing each time period (sections at room temperature, incubator temperature and icebox temperature), as may be noted from the "combined" tracings in figures 1 and 2.

In our search of the literature for reports of work on this problem, the only paper we have been able to study is one by Jolly in the French,

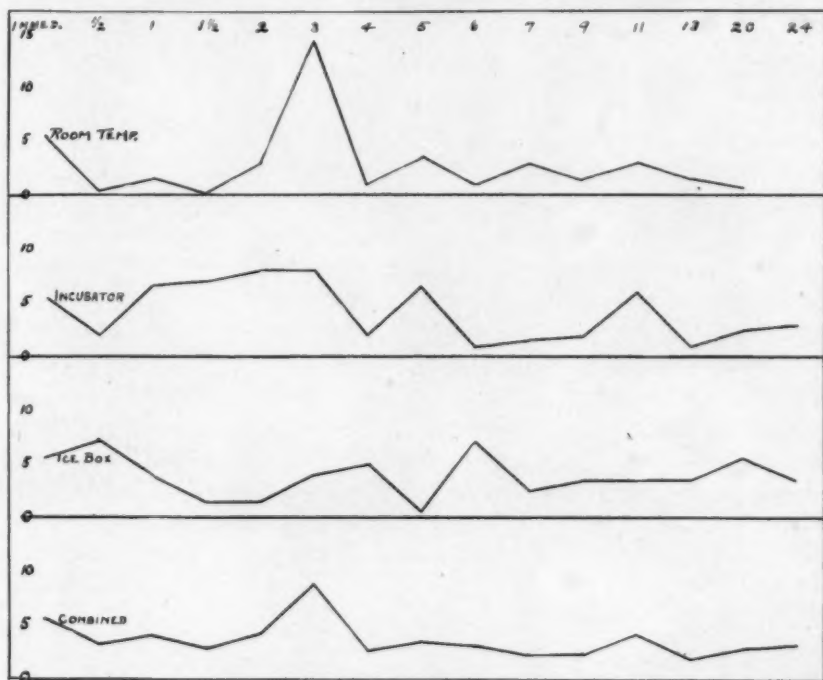


Chart 2 (case 2).—Same observations as in chart 1.

in 1910.³ He presents a rather extended report of observations on various animals and tissues and concludes that there is only a slight decrease in the numbers of mitotic figures at the end of twenty-four hours and a somewhat greater decrease by the end of forty-eight hours.

Our own observations do not extend beyond the twenty-four hour period.

CONCLUSIONS

Our counts show that during the time from the removal of the tumor up to twenty-four hours, there is no material variation in the number of mitotic figures found in the tissue. This is true for the

3. Jolly, J.: *Compt. rend. Soc. de biol.* **69** (Dec. 14) 1910.

tissue kept under the three different conditions of temperature, room temperature, icebox and incubator. There is, however, in each case evidently a slight drop in the numbers present.

If it should prove that observation of other malignant tumors coincides with our results in these two tumors one would be justified in the opinion that in tissue handled as most tumor specimens are, the delay of a few hours after removal of the specimen before fixation has no practical influence on the mitotic figure count and so does not vitiate interpretation based on these counts.

MALIGNANT ANGIOMAS

WITH REFERENCE TO THE QUESTION OF SARCOMA
DUE TO ROENTGEN RAY *

S. F. LIVINGSTON, M.D.

AND

PAUL KLEMPERER, M.D.

NEW YORK

Angiomas may be defined as new-growths consisting largely of newly formed blood and lymph vessels originating from angioblastic tissue. According to Ribbert,¹ the hemangioma develops from a circumscribed vascular area which has not properly adapted itself to its environment because of developmental disturbances. However, new formation of blood vessels is not only found in angiomas, but it constitutes one of the prominent features of granulation tissue. Therefore the differentiation between neoplastic proliferation of blood vessels and new formation in hypertrophic granulation tissue offers considerable difficulty in histologic diagnosis. Two cases have been observed by us which illustrate this difficulty. One case presented a microscopic picture apparently that of a malignant tumor, whereas the clinical picture was rather insignificant. The second case, considered at first microscopically as granulation tissue, clinically was that of an aggressive malignant neoplasm.

The pathogenesis of the first case bears an intimate relationship to previous roentgenotherapy.

CASE 1.—Mrs. M. W., white, aged 28, married, mother of one child, was first seen by Dr. E. W. Peterson, Feb. 12, 1920, to whom we are greatly indebted for the clinical history of the case. The family history was negative. The past history was irrelevant except for one miscarriage. She came to Dr. Peterson complaining of scar tissue on her neck, with the following history: In 1915, she received monthly roentgen-ray treatment for hypertrichosis of the chin, over a period of seven months. When first seen, she showed a keloid-like thickening with superficial ulceration of the skin in the region of the thyroid cartilage. The skin over both mandibles was tense and shiny. On May 11, 1920, the scar was completely excised and the defect covered by Thiersch graft. The pathologic report by Dr. W. J. MacNeal was that of chronic inflammation with central ulceration.

On Dec. 13, 1922, the patient returned with a nodule underneath the skin near the original scar. The nodule and the overlying skin were excised. The gross description by Dr. MacNeal was as follows: "The specimen measures

* Read before the New York Pathological Society, Jan. 12, 1926.

* From the Department of the Laboratories, New York Post-Graduate Medical School and Hospital.

1. Ribbert, H.: *Geschwulstlehre*, Bonn, Friederich Cohen, 1904, p. 169.

32 by 27 by 23 mm. On section there is a reddish purple, round mass in the interior about 16 mm. in diameter. There is an attached piece of skin 25 by 10 mm. in area." The microscopic description will be given later. A diagnosis of angioblastic sarcoma was made.

On Sept. 17, 1923, a flat, purplish nodule developed on the left side of the neck. This was excised together with a wide margin of healthy skin surrounding it. The histologic picture was identical with that of the previous specimen, and the diagnosis of angioblastic sarcoma was made again.

On June 24, 1924, there appeared on both sides of the neck flat patches which can best be described as resembling nevi vasculosi. An attempt was made to prevent the recurrence of these areas by very wide surgical excision. Radium treatment was suggested, but by agreement of several competent authorities was

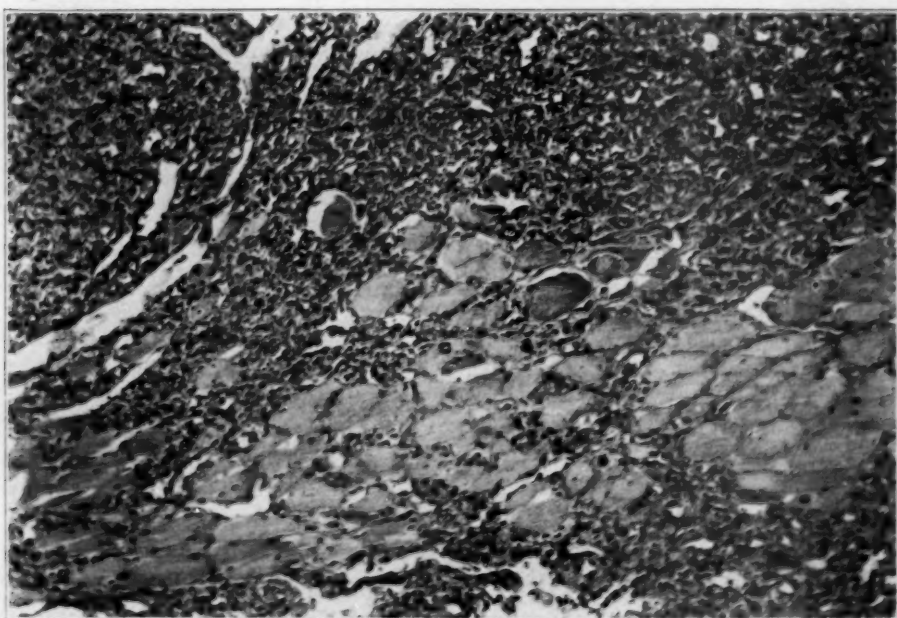


Fig. 1 (case 1).—A cellular node within the subcutis. Spindle cells infiltrating striated muscle. Numerous cross and longitudinal sections of capillaries; $\times 80$.

not applied; but, contrary to advice, in the summer of 1924, the patient went to a radium institute for treatment. The exact dosage given is unknown to us.

On Dec. 30, 1924, a recurrence of new lesions on both sides of the neck were again excised. Several skin flaps were obtained for microscopic study. These were irregular in outline with numerous ill-defined flat spots of dusky red. On section, the redness appeared to be due to red nodules within the corium. A portion of the subcutaneous tissue overlying a salivary gland was excised, and it showed a similar lesion.

On March 16, 1925, and on May 13, 1925, similar lesions developed and were excised. Following this the patient received several treatments with Coley's serum. During the summer of 1925, the patient was seen by several prominent authorities, who agreed that all surgical intervention should be discontinued. The opinion was expressed that the patient was suffering from "too much surgery,"

and that the skin, if left alone for a sufficient period of time, would heal. Further report of her condition during the early fall is rather vague. During the last few months of her life the patient developed a wide and deep ulceration on the left side of her neck, which invaded the tissues extensively, exposing the large vessels. The patient died in December, 1925. Necropsy was not obtained.

From the various operations, cutaneous flaps, including the red spots, were submitted for histologic examination, which presented a fairly uniform picture throughout. A study of the histology of the specimens showed that the epidermis was rather thin, covering the papillary layer which was flattened. In the deeper areas of the corium occasional hair follicles, sporadic sweat and sebaceous glands

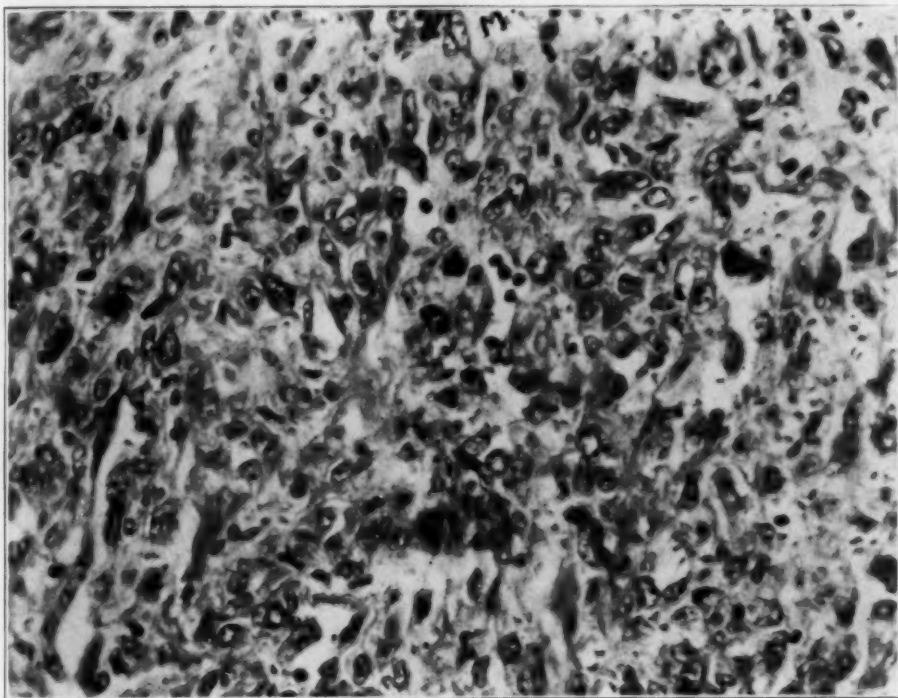


Fig. 2 (case 1).—Spindle cells lining blood capillaries. *M* indicates mitotic division figure; $\times 500$.

were found. The stroma consisted of dense connective tissue with a few smooth muscle bundles and conspicuous dilated capillaries lined by endothelial cells, many of which were considerably enlarged. In the subcutaneous fat there was an ill-defined area extending into the underlying striated muscle as well as into the surrounding fat and connective tissue. Such areas were found in practically every section removed at the different operations. They consisted chiefly of large spindle cells and a number of small round cells. There was an abundance of wide capillaries and a very scant, fine fibrillar stroma, as evidenced by Mallory's orange G-fuchsin stain. The component cells infiltrated the adjacent muscle tissue compressing the bundles with resulting atrophy (fig. 1). By high-power examination (fig. 2), it was easily recognized that the spindle cells contained an oval-shaped pale nucleus with nucleolus and constituted the endothelial lining of

the small capillaries. Many nuclei were conspicuous by their deeper stain, and frequently mitotic figures were encountered. There was an occasional lymphocyte and polymorphonuclear leukocyte mingled with red blood cells, between and within the lumina of the blood spaces. Similar pictures were found in the histologic examination of the cutaneous red spots in every instance.

In the corium of the skin flap removed at the second operation several small islands formed by dilated capillaries sprouting in various directions were found (figs. 3 and 4). These capillaries were well developed, and they, as well as the distended blood spaces, were lined by endothelial cells frequently of large size. In the adjacent corium, there were numerous isolated telangiectatic capillaries as described above.

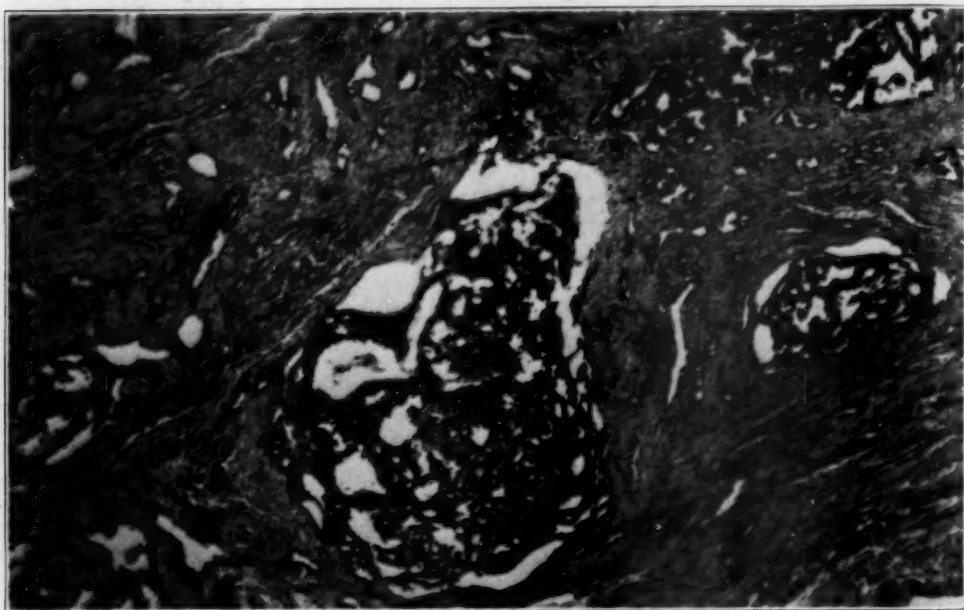


Fig. 3 (case 1).—Angiomatous nodules within the cutis; $\times 57$.

The predominating histologic feature of the various specimens removed during a period of nearly three years was the extensive proliferation of the blood capillaries. The question arises "Are we dealing with a tumor or granulation tissue?" According to Ewing's² definition, hypertrophic granulation tissue presents an extensive new-growth of vessels. It is self-limited and regresses on the removal of the irritant. It is conceivable that the irritant in this case may have been the surgical traumatism to a skin damaged by previous radiation, the latter being evidenced by the atrophy of the skin. Yet it seems difficult to

2. Ewing, James: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, ed. 2, 1922.

conceive that the irritation always produces the same picture of atypical granulation tissue with proliferation of the vascular elements exclusively. This argues against the interpretation of the lesion as only that of granulation tissue. The repeated recurrence, after the wide excision, the histologic evidence of infiltrative growth into fat and muscle tissue, and lastly the fatal outcome, are strong arguments in favor of the diagnosis of an angioblastic sarcoma. We are, however, perfectly con-

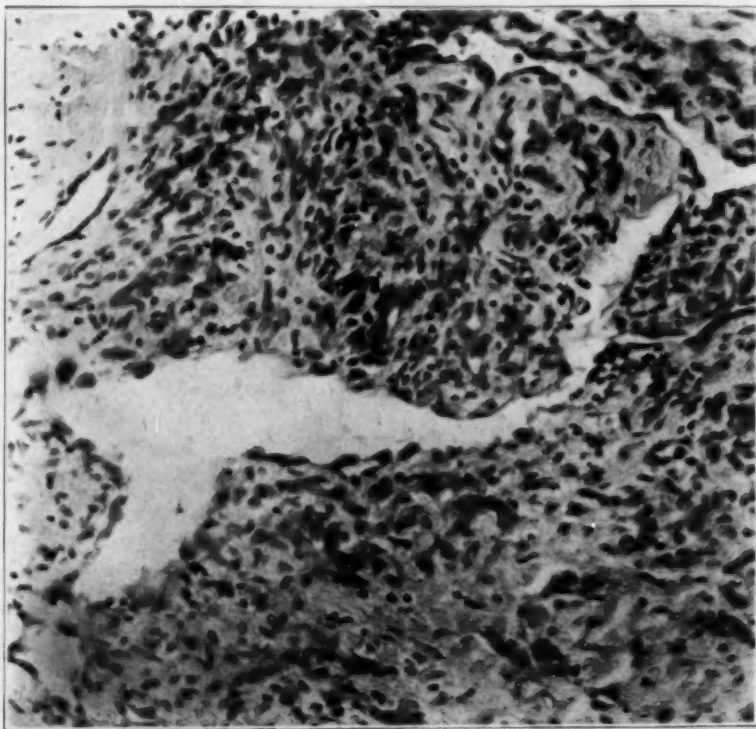


Fig. 4 (case 1).—Proliferation of new capillaries from telangiectasia; $\times 220$.

scious of the fact that the ultimate criteria for the diagnosis of a malignant tumor are lacking, since no metastases could be demonstrated.

A thorough review of the literature available reveals only one similar case, reported by Ehrmann³ in 1902. His patient was a woman who had been treated several times with roentgen rays for the removal of hypertrichosis. Two years previous to the demonstration of the patient, an ulcer had appeared which had healed. At the time of the report, multiple hemangiomas could be seen which impressed one as naevi vasculosi disseminati. There was no histologic report.

3. Ehrmann, S.: Wiener Gesellschaft der Ärzte, 1902, Ref. Fortschritte auf dem Gebiete der Röntgenstrahlen 5:362, 1901-1902.

The relation between the roentgen rays and sarcoma formation is by no means as definitely established as that of the development of carcinoma from roentgen-ray injury. Hesse⁴ in his review of the symptomatology, pathogenesis and therapy of the roentgen carcinoma from the year 1911, refers only to one case of true spindle cell sarcoma reported by Unna.⁵ This case occurred in a patient with roentgen carcinoma. The other cases were not clear-cut, and therefore not accepted as such. It is noteworthy that Mallory, in a case of roentgen-

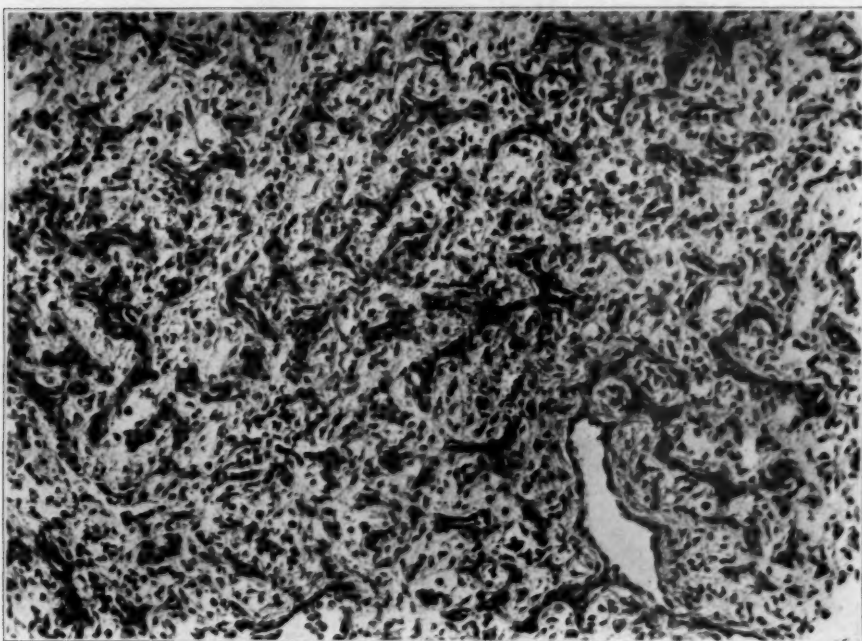


Fig. 5 (case 2).—Angiomatous portion with narrow capillaries; $\times 120$.

ray injury in a laborer, hesitated between a diagnosis of fibrosarcoma and an unusual reparative process, because no previous authentic case of roentgen-ray sarcoma had been on record. Since 1911, several articles have tried to correlate roentgen-ray injury and sarcoma formation. Marsch⁶ reports two cases and Beck⁷ five cases of osteosarcoma and enchondroma on the basis of tuberculosis after previous prolonged roentgen-ray treatment. In these cases there is only indirect evidence

4. Hesse, O.: *Zwanglose Abhandlungen aus dem Gebiete der Mediz., Elek. trologie und Roentgendkunde*, 1911, pt. 10, p. 1.

5. Unna, P. G.: *Fortschr. a. d. Geb. der Röntgenstrahlen* 8:67, 1904-1905.

6. Marsch, E.: *Zentralbl. f. Chir.* 49:1057, 1922.

7. Beck, A.: *München. Med. Wchnschr.* 69:623, 1922; *Deutsche Ztschr. f. Chir.* 186:255, 1924.

which speaks for a pathogenic correlation between sarcoma formation and antecedent roentgen-ray treatment. We were able to trace the atypical blood vessel proliferation back to the endothelial lining of cutaneous telangiectasis which constituted one of the well-known features of skin lesions produced by the roentgen ray.⁸ The etiologic relationship between atypical vascular proliferation and previous radiation suggested by the clinical picture has been established beyond doubt by the histologic evidence.

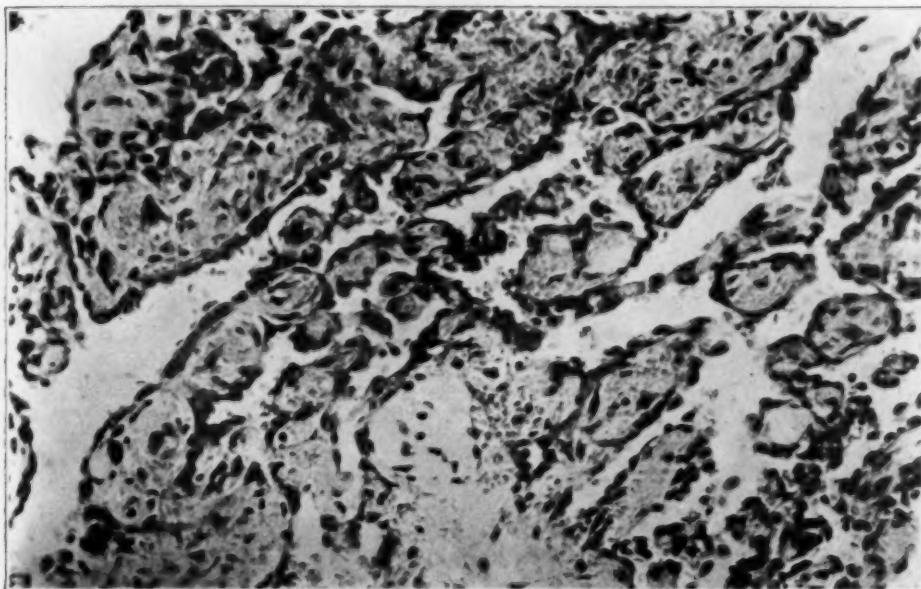


Fig. 6 (case 2).—Sinuses with knoblike stroma projections; $\times 220$.

CASE 2.—M. S., a man, aged 38, was admitted to the hospital February, 1925, in the service of Dr. J. F. Erdman, to whom we are indebted for the clinical history of the case. His chief complaint was a recurrent tumor of the scalp. The family history was essentially negative. About three months prior to admission, the patient noticed a lump growing on the right side of the scalp. This grew rapidly and caused dull pain throughout the head. The tumor was incised at a dispensary. Since then (one month prior to admission) it has grown more rapidly and bleeds profusely. The general physical examination is essentially negative. Local physical examination revealed a large tumor mass about 3 cm. in diameter situated on the right side of the scalp, fixed to the skin and adherent to the bone posteriorly. There was definite fluctuation in the center.

The tumor was excised after much difficulty because of excessive hemorrhage. It was found to have invaded and destroyed the underlying bone. The wound

8. Freund, L., and Oppenheimer, M.: *Wien. klin. Wchnschr.* **17**:333, 1904. Rost, G. A.: *Strahlentherapie* **6**:269, 1915. Peterson and Hellman: *Strahlentherapie* **11**:474, 1920.

was packed with iodoform gauze. During the stay in the hospital, the patient had an uneventful course except that with each dressing of the wound profuse hemorrhage followed. He was discharged three weeks after admission. The patient was free from symptoms for four and one-half weeks following discharge from the hospital. On the occasion of a dressing of his wound he had a profuse hemorrhage. On May 23, 1925, he was admitted to another hospital for severe hemorrhage from the scalp. It was impossible to control bleeding, and the patient finally died six days after admission.

In the histologic examination one is impressed by two outstanding pictures which freely merge with each other and constitute the characteristic structures of the tumor. One prominent feature is the presence of blood capillaries and blood sinuses, which capillaries formed a regular network and lay within a cellular



Fig. 7 (case 2).—Undifferentiated portions of tumor; $\times 120$.

stroma of loose fibrillar tissue. The narrow lumen of the capillaries was lined by large spindle-shaped endothelial cells (fig. 5). Some of the capillaries contained red blood cells. The most characteristic feature of the cavernous portion of the tumor were knoblike projections of the surrounding stroma which protruded into the sinuses and were covered with large endothelial cells (fig. 6). The surrounding stroma and the knoblike projections were composed of a fibrillar tissue with scant cellular elements. The fibrillae frequently formed whorls and occasionally were coarse and homogeneous like hyaline fibrillae. Other parts of the tumor impressed one, on low-power examination, as being composed of fibrillar tissue in which long spindle-shaped cells formed a characteristic part, and could best be compared to edematous granulation tissue (fig. 7). Only occasionally blood capillaries or wider sinuses were seen. It must be emphasized, however, that the stroma of the vascular areas described above showed, on closer examination, a great similarity to the avascular portions. On the other hand, the number of capillaries varied

considerably, and portions with a greater number of capillaries formed a link between the vascular and avascular portions of the tumor. Most of these portions contained numerous erythrocytes.

On high-power examination, the matrix was seen to consist of loosely arranged, wavy, very fine fibrillae, which stained a faint pink with van Gieson stain. Suspended in this ground substance, or matrix, there were very long spindle-shaped cells with oval, pale nuclei, frequently forming a loose network (fig. 8). Here and there mitotic figures were seen in these cells. Occasionally unusually large spindle cells with abundant cytoplasm occurred, and frequently syncytia-like formations with cells containing several nuclei identical to the nuclei of the cells described before. It was not uncommon to find in these syncytia a slitlike lumen which occasionally contained a few red blood cells (fig. 9). Blood capillaries

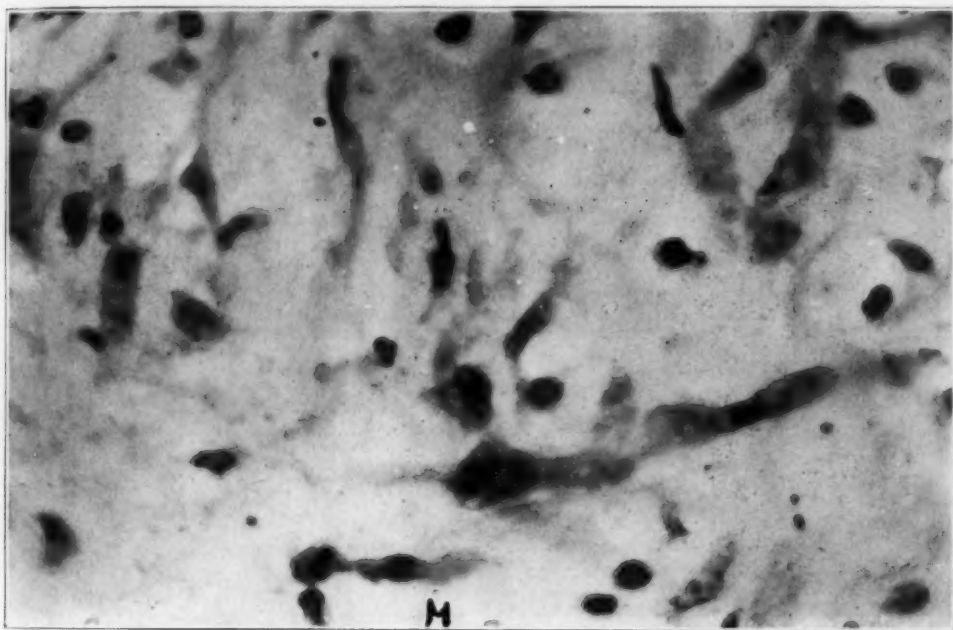


Fig. 8 (case 2).—A loose network of large spindle cells. *M* indicates mitotic division figure; $\times 760$.

lined with a single row of cells with similar nuclei and without definite cell borders were seen in cross and longitudinal sections. Proliferation in these syncytia was indicated by the presence of mitotic division figures (fig. 10). Aside from these cells and structures which formed the predominant part, there were numerous erythrocytes and occasional round cells with an abundant cytoplasm and a dark round nucleus. A few polymorphonuclear leukocytes and lymphocytes were found in the stroma and the larger vascular spaces.

Summarizing our findings, we have a tumor originating in the scalp, growing rapidly and destroying the underlying bone of the skull, which could not be completely excised by operation and produced severe

hemorrhage, terminating the life of the patient. The histologic picture of the tumor was misleading. Because of the proliferation of fine capillaries in an undifferentiated tissue, the diagnosis of granulation tissue was made. A correct diagnosis was made only when the angiomatous portions with the characteristic features of an intracanalicular type of fibroangioma (Borst⁹) were found.

The picture of the sinuses with the knoblike stroma projections (fig. 6) duplicates the plates of Borrmann's¹⁰ case of a metastasizing angioma. Besides the case of Borrmann only two similar cases have

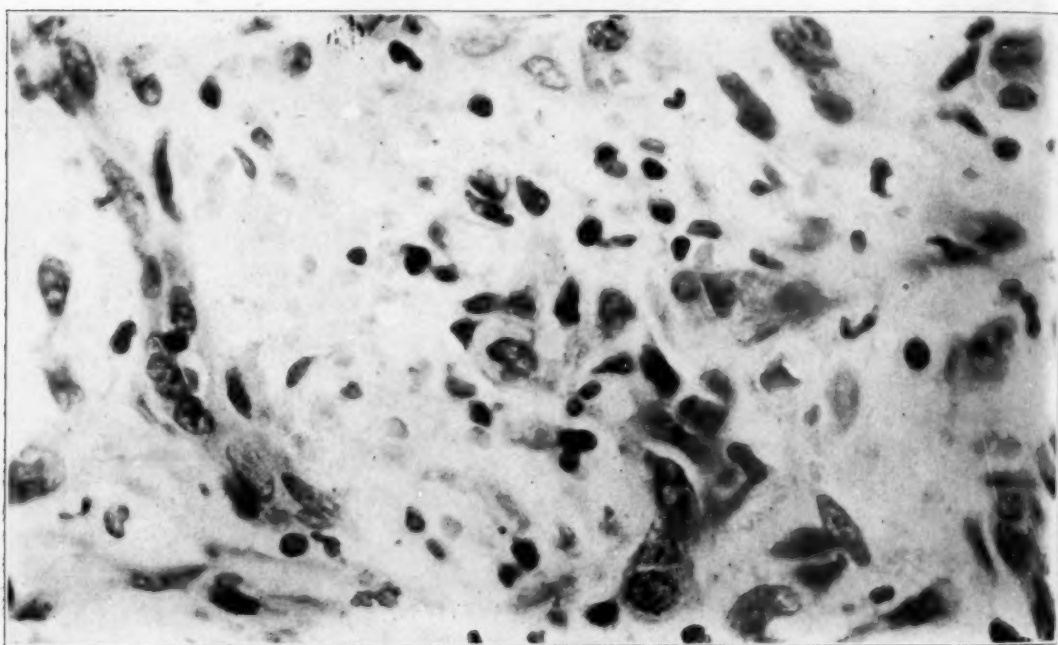


Fig. 9 (case 2).—Syncytia with beginning formation of lumina; $\times 760$.

been found in the literature (Shennan¹¹ and Ewing¹²). These three cases have produced metastases, thereby proving their malignancy beyond doubt. Although, in our case, metastasis formation could not be demonstrated because necropsy was not obtained, sufficient evidence of malignancy is brought forward by the rapid growth and the exten-

9. Borst, in Aschoff, Ludwig: *Pathologische Anatomie*, ed. 6, 1:688, Jena, Gustav Fischer, 1923.

10. Borrmann, R.: *Beitr. z. path. Anat. u. z. allg. Pathol.* 40:372, 1907.

11. Shennan, Theodor: *J. Path. & Bact.* 19:139, 1914-1915.

12. Ewing, James: *Neoplastic Diseases*, ed. 2, Philadelphia, W. B. Saunders Company, 1922.

sive destruction of the bone. Borrmann and other observers consider this type of neoplasm as a malignant angioma with a histologically benign picture. We cannot follow the authors in this interpretation. Borrmann emphasizes that nowhere was there evidence of sarcomatous portions which would designate the neoplasm as an angioma sarcomatosum. We agree with Borrmann's description which could be applied to our case. We cannot agree, however, with his interpretation of the stroma as merely connective tissue. The peculiar syncytial structures which developed blood capillaries reminded us strongly of the vaso-

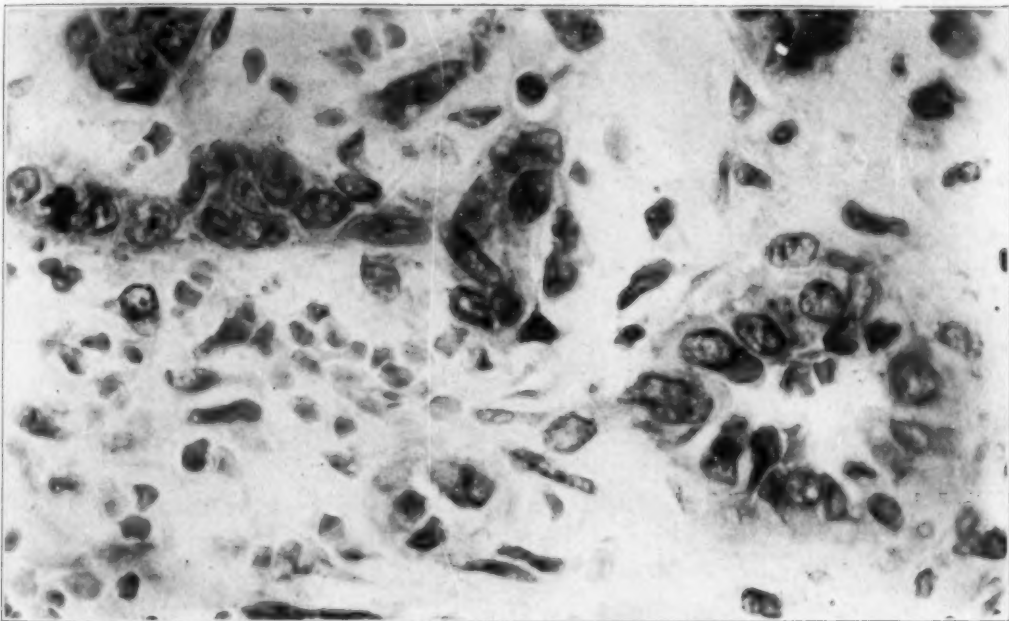


Fig. 10 (case 2).—Syncytium, left; blood capillary, right. Note the mitotic division figures in both; $\times 760$.

formative cells of the mesenchyme. The fine fibrillar matrix in which a network of long spindle cells is suspended is well known from the appearance to be that of embryonal connective tissue. Granulation tissue more than any structure of the adult organism has the greatest similarity with mesenchyme. It is not mere incident that the first diagnosis in our case was vascular granulation tissue, since the aggressive neoplastic character of the growth was not known.

We conceive, therefore, our tumor as a neoplasm composed of mesenchyme of varying stages of differentiation. The avascular stroma must be considered as the most unripe phase. The sinuses with the knoblike projections constitute the highest differentiation attained

by the vasoformative elements. Between these extremes we encounter all phases of the development of blood vessels originating from angioblastic cells. With that interpretation, the difference between the malignant course of the tumor and its apparently benign histologic picture can easily be reconciled.

The occurrence of malignant tumors composed of undifferentiated mesenchymal tissue has been reported by Ernst-Falkowsky,¹³ Klinge¹⁴ and others. It is interesting to note that in these cases the mesenchymal constituent was recognized only after extensive search. In both cases, which showed the characteristics of malignant tumors, the angiomatous portions overshadowed the blastomatous mesenchymal component. In discussing case reports of malignant angiomas, Klinge considers the question as to whether Borrmann's case might not have been an unripe mesenchymal blastoma with predominance of angiomatous structures. It seems to us that Klinge's question can be answered in the affirmative on the strength of our observation in an identical case. The clinical and histologic similarities of our case with three cases in the literature indicate that these tumors form a group by themselves. Since their histologically benign nature cannot be accepted any more, the term "malignant mesenchymal angioma" as proposed by Klinge, is recommended. This term expresses the simultaneous presence of undifferentiated mesenchymal and angiomatous structures in a malignant tumor.

SUMMARY

1. A case of recurrent naevi vasculosi is reported.
2. The histologic examination revealed features highly suggestive of an angioblastic sarcoma.
3. The microscopic picture revealed definite evidence of a pathogenetic relationship between the atypical vascular proliferation and the previous roentgen-ray treatment.
4. A case of a malignant angioma with apparently benign histologic features is reported.
5. The histologic examination reveals unripe mesenchymal tissue as a constituent of the tumor which explains the malignant nature of this type of neoplasm.

13. Ernst-Falkowsky: Beitr. z. path. Anat. u. allg. Pathol. **57**:385, 1914.

14. Klinge, F.: Deutsche Ztschr. f. Chir. **183**:195, 1923.

EXPERIMENTAL FOCAL EMBOLIC GLOMERULONEPHRITIS IN RABBITS *

B. J. CLAWSON, M.D.

MINNEAPOLIS

Focal embolic glomerulonephritis was first described by Löhlein¹ in 1910 and subsequently by Baehr² in 1912. It differs from the diffuse form of glomerulonephritis in that many glomeruli, usually a majority, are unaffected. The glomeruli involved usually show only a portion of the tuft affected. Both exudative and proliferative processes occur, and some glomeruli are completely closed by the inflammatory process.

The close association of this glomerular injury to subacute bacterial endocarditis has been discussed by Löhlein,¹ Baehr,² Warwick³ and others. It is one of the embolic phenomena commonly found in bacterial endocarditis, and the resulting hematuria is an important diagnostic finding. With rare exceptions, this renal lesion is always associated with subacute bacterial endocarditis.

It is generally believed that the lesions in the glomeruli of the kidneys in focal embolic glomerulonephritis are produced by particles of thrombi containing bacteria breaking off from vegetations on the heart valve. Baehr thinks that the tendency for the streptococci to clump together is an important factor in the production of the characteristic glomerular lesions.

METHOD

Two conditions were necessary to simulate the condition found in the arterial blood in subacute bacterial endocarditis: (1) to have floating in the blood stream very small particles containing masses of streptococci similar to the particles of thrombi from the heart valves, and (2) to have these particles in the arterial system. To meet the first condition, plain agar was heavily seeded with *Streptococcus viridans* and incubated at 37 C. for twenty-four hours. The organism used was a strain isolated from the blood of a patient having acute rheumatic endocarditis. The agar with the organisms was ground in a mortar

* From the Department of Pathology, University of Minnesota.

1. Löhlein: Ueber hämorrhagische Nierenaffektionen bei chronischer ulzeröser Endokarditis, Med. Klin. **6**:375, 1910.

2. Baehr, G.: Glomerular Lesions of Subacute Bacterial Endocarditis, J. Exper. Med. **15**:330, 1912; Am. J. M. Sc. **144**:327, 1912; The Significance of the Embolic Glomerular Lesions of Subacute Streptococcus Endocarditis, Arch. Int. Med. **27**:262, 1921.

3. Warwick, M.: Focal Embolic Glomerulonephritis, J. Lab. & Clin. Med. **7**:507, 1922.

with salt solution until a fine suspension was formed. The coarser particles of agar were thrown out of the suspension by centrifugalization. Suspensions of streptococci which had been agglutinated by a specific serum were also used.

To meet the second condition the supernatant suspension of streptococci and agar or the suspension of agglutinated streptococci was injected intracardially into the cavity of the left ventricle. At first, the mortality from cerebral emboli was high, but this was reduced to a minimum by using smaller particles of agar in the suspension. Cerebral emboli seldom occurred with agglutinated streptococci. Repeated injections were made at intervals of about ten days. Many injections may be made without seriously injuring the myocardium.

TABLE 1.—Results Obtained by Injecting Streptococci in Agar

Num- ber	Dura- tion, Days	Num- ber of Injec- tions	In- farcts	Em- boli in Artery	Em- boli in Tufts	Glom- erular Exuda- tion	Intra- capil- lary Prolif- eration	Epi- thelial Cres- cents	Hya- liniza- tion	Pus in Tubules	Tub- ular Atro- phy	Percent- age of Glom- eruli Injured
1	1	1	+	+	+	+	0	0	0	+	0	8
2	1	1	0	+	+	+	0	0	0	0	0	10
3	2	1	0	+	+	+	0	0	0	0	0	5
4	3	1	0	+	+	+	0	0	0	0	0	12
5	4	1	0	+	+	+	+	0	+	0	0	10
6	6	2	+	+	+	0	0	0	0	0	0	4
7	6	1	+	+	+	0	+	+	0	0	0	7
8	7	3	+	+	+	+	0	0	0	0	0	5
9	11	2	0	+	+	0	+	0	0	0	0	7
10	13	2	+	+	+	+	+	+	+	0	0	13
11	14	2	0	+	+	0	0	0	0	0	0	3
12	25	3	0	+	+	+	+	+	+	+	+	14
13	30	3	+	+	+	+	+	+	+	+	+	32
14	36	5	+	+	+	+	+	+	+	+	+	45

ANIMAL EXPERIMENTS

Two series of experiments were performed. In the first series each rabbit received intracardial injections with about 5 cc. of a suspension of streptococci and agar. In the second series each rabbit received intracardial injections with about the same amount of a suspension of agglutinated streptococci.

The results of the inoculations with the streptococci in agar are given in table 1. Fourteen rabbits were inoculated from one to five times. The length of life of the rabbits ranged from one to thirty-six days. Gross or microscopic kidney infarcts were fairly common, being present in half of the animals. In all cases agar emboli were found in some of the afferent arteries of the glomeruli and within some of the tufts. In some glomeruli, clumps of bacteria forming emboli could be seen. Exudation of polymorphonuclear leukocytes replacing part or all of the tuft in some glomeruli was seen in ten of the fourteen cases. Proliferation of the endothelial cells of the glomeruli was noted in six of the fourteen cases (figs. 1, 2 and 3). This proliferation was observed in animals dying as soon as four days after the first injection. Proliferation of Bowman's capsule to form epithelial crescents occurred in five of the fourteen cases. The earliest occurrence of these crescents was six days after the first injection. Hyalinization of the content of the glomerular tuft was seen in five of the fourteen. It occurred as

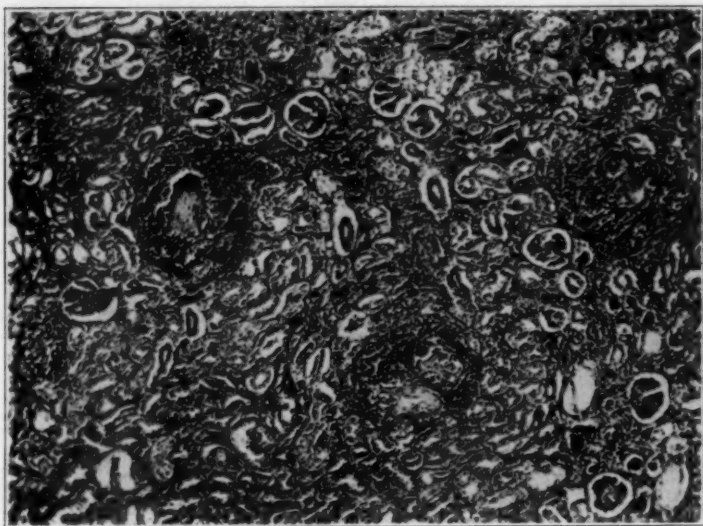


Fig. 1.—Glomeruli showing proliferation.

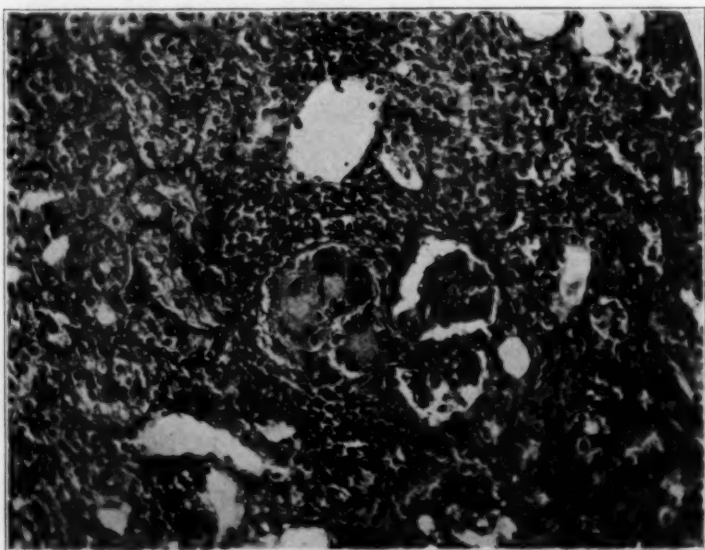


Fig. 2.—A glomerulus with proliferation of part of the tuft.

soon as four days after the injection. Pus cells were seen in some of the tubules. Atrophy of tubules was apparent in only three of the fourteen cases, and its earliest occurrence after the first injection was twenty-five days. The involvement of the glomeruli ranged approximately from 4 to 45 per cent. The rabbit showing an injury to 45 per cent of its glomeruli lived thirty-six days after the first inoculation and received five injections.

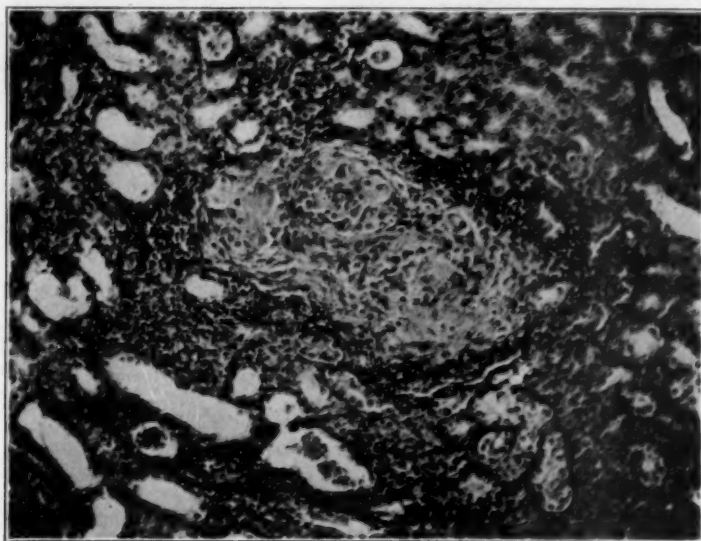


Fig. 3.—A glomerulus with proliferation of endothelial cells in entire tuft.

TABLE 2.—Results Obtained by Injecting Agglutinated *Streptococci*

Number	Duration, Days	Number of Injections	In-farcts	Em-boli in Artery	Em-boli in Tufts	Glom-erular Exuda-tion	Intra-capil-lary Prolif-eration	Epi-thelial Cres-cents	Hya-liniza-tion	Pus in Tubules	Tub-ular Atro-phy	Percent-age of Glom-eruli Injured
1	1	1	0	0	0	0	0	0	0	0	0	0
2	1	1	+	0	0	0	0	0	0	0	0	0
3	1	1	0	0	0	0	0	0	0	0	0	0
4	3	1	0	0	0	0	0	0	0	0	0	0
5	3	1	+	0	0	0	0	0	0	0	0	0
6	3	1	+	0	0	0	0	0	0	0	0	0
7	4	1	+	0	0	0	0	0	0	0	0	0
8	5	1	0	0	0	0	0	0	0	0	0	0
9	6	2	+	0	0	0	0	0	0	0	0	0
10	7	1	+	0	0	0	0	0	0	0	0	0
11	7	2	0	0	0	0	+	0	0	0	0	1
12	7	1	+	+	+	+	+	0	0	0	0	2
13	8	1	+	+	+	+	+	0	+	0	0	1
14	9	3	+	+	+	+	+	+	+	0	0	4
15	17	4	0	0	0	0	0	0	0	0	0	0
16	29	4	0	0	0	0	0	0	0	0	0	0

In these fourteen cases, practically all stages of injury are seen occurring in part of the same glomeruli or in all the tufts of different glomeruli, a condition which is characteristic of focal embolic glomerulonephritis associated with subacute bacterial endocarditis.

The sixteen rabbits that received injections with agglutinated streptococci showed much less glomerular injury than was found in the rabbits injected with streptococci in agar (table 2). Infarction was of frequent occurrence. Glomerular changes were present in four of the sixteen rabbits. Both exudative and proliferative changes were noted. Epithelial crescents were found in only one case; hyalinized glomeruli were seen in two. Atrophy of tubules did not occur. Four per cent of the glomeruli was the highest involvement found in any animal.

SUMMARY

These experiments illustrate a method for making inoculations directly into the arterial system and show that focal embolic glomerulonephritis, similar to that associated with human subacute bacterial endocarditis, can be produced experimentally in rabbits.

Laboratory and Technical Notes

A NEW METHOD OF MOUNTING FIXED FROZEN SECTIONS*

LENORE D. CAMPBELL, M.D., LOMA LINDA, CALIF.

In places where large numbers of frozen sections are used, as for a class of students, a method which saves time and nervous energy is most welcome. In this laboratory frozen sections are used as a routine. Only a few friable tissues, such as lung, pancreas or mucosae, are run through paraffin; occasionally



Fig. 1.—Lifting out of water.



Fig. 2.—Holding in alcohol.



Fig. 3.—Floating off on surface of water.



Fig. 4.—Mounting on slide.

some are blocked for special staining methods. The method described below has been found useful for all except very ragged tissues, as it is easier, quicker and gives smoother mounts than the old method of pulling the section up on the slide with a section lifter. It has possibly been used by others, but to my knowledge it has not appeared in print.

*From the Pathology Laboratory, College of Medical Evangelists, Loma Linda, Calif.

It is easier to work over a black table. The steps are as follows:

1. Previously fixed tissues are cut with a freezing microtome 7 to 12 microns thick, placing the sections in a large glass dish containing water.

2. A section is lifted out with a glass rod with the section wrapped smoothly around the rod near its end, and held in 95 per cent alcohol for two or three seconds.

3. The section is returned to a large, deep staining dish of water (about 7 cm. deep), unrolling the section from the rod on top of water. In most cases it will float on the surface and be perfectly smooth.

4. A glass slide is brought against one edge of the floating section, holding the slide at almost right angles to the surface, and is lifted out. The section will adhere to the slide. If it has not been held in alcohol sufficiently long, or if too much time elapses before mounting after returning to the water, it will sink beneath the surface and cannot be readily mounted. If a fold should occur, the slide should be held on the edge and dipped carefully up and down in the water (not immersing the entire section), and the fold will easily be removed.

5. The mount is completed as usual by dropping on 95 per cent alcohol to dehydrate. It is blotted with a smooth folded cloth, and very thin celloidin is dropped on the section, holding the slide almost perpendicular to the table.

When the celloidin begins to solidify it is to be stained as desired.

General Review

EXPERIMENTAL INFECTION-IMMUNIZATION AGAINST TUBERCULOSIS *

ESMOND R. LONG, PH.D.

CHICAGO

Before the discovery of the tubercle bacillus and the immense amount of research stimulated thereby, clinical observation recognized no immunity in tuberculosis. Apparently patients with this disease could not recover, or in rare instances recovered only to succumb to a second assault. The first clinically recognized attack seemed to fail utterly to confer that immunity which, as clinical observation showed, operated so effectively against infections with the virus of typhoid fever or smallpox.

In 1886, however, Marfan¹ described what at first appeared to be a paradox, immunity toward consumption conferred by the cure of a local tuberculous lesion. Marfan was interested in lupus and certain forms of cervical adenitis, and concerned in proving in the light of the recent discovery of the tubercle bacillus that these were forms of tuberculosis. In the course of his investigation he was more and more impressed by the infrequency with which tuberculosis of the lungs developed in adults who had recovered from tuberculosis of the skin or lymph nodes. He was led to publish what has since become known as the "law" of Marfan: "Manifest and progressive pulmonary tuberculosis are almost never found in persons who, during childhood, have had a suppurative tuberculous adenitis of the neck, and who have been completely cured of it before the age of 15 years and before any other focus of tuberculosis was appreciable."

Clinical and postmortem evidence have long since repeatedly established the essential validity of the law of Marfan. After the first burst of astonishment over the observations of Naegeli in the dead horse and the results of Pirquet, Hamburger, Mantoux, Moro and Petruschky with the tuberculin reaction, the medical profession rapidly came to appreciate the great extent of tuberculous infection in childhood and near universality in adults, and accept the doctrine that early tuberculosis is in some measure protective against reinfection in later years.

Long before this truth was realized, however, within a year, in fact, after the discovery of the tubercle bacillus, attempts were made to create immunity artificially in experimental animals. The success of Pasteur with attenuated anthrax and chicken cholera germs had prepared the

* From the Department of Pathology of the University of Chicago.

1. Marfan, A.: De l'immunité conférée par la guérison d'une tuberculose locale pour la phthise pulmonaire, Arch. gén. de méd. 17:423, 575, 1886.

way, the example of Jenner was a constant stimulus, and vaccination was already a favorite field of investigation. Soon dead tubercle bacilli, attenuated tubercle bacilli, virulent tubercle bacilli in small numbers and tubercle bacilli modified in scores of unusual ways, as well as innumerable fractions of the bacillus isolated by chemical means, were being tested as specific prophylaxis against tuberculosis in laboratory animals. It is significant that among the very first studies were experiments on the immunizing properties of living tubercle bacilli. Immunity following actual infection was an unescapable clinical fact in the case of other diseases, and years before the weight of an enormous literature bore out their contention, this more dangerous method of immunizing appeared to many early investigators more likely to be effective than the use of specific material, made harmless by heat, chemicals or other means.

It would be futile to attempt to recognize priority in this field. The earliest experiments were failures, and some of the successes described shortly afterward were based on too scanty experimentation to be conclusive. Among the first sustained investigations were those carried out in this country by Trudeau, and Trudeau's influence is reflected in the trend of research in this country today. In his articles may be found references to the early efforts of Falk (1883), Martin and Grancher, Courmont and Dor, Kitasato, Dixon and others, to produce immunity experimentally. Other early literature, as well as much of that which has appeared since, including many references not cited in this article, is covered in excellent reviews by Löwenstein,² Römer (1910)³ and Baldwin and Gardner (1921).⁴

Trudeau⁵ attempted to immunize animals with living tubercle bacilli, first with avian bacilli and later with attenuated human type bacilli, in the hope that these organisms of low virulence, which could be safely inoculated in small doses, would produce a resistance to reinfection with organisms of high virulence. In his first experiments it developed that rabbits which had survived the subcutaneous inoculation of living avian bacilli in graded doses, acquired a certain degree of immunity toward subsequent inoculation of the eye with cultures of bacilli of the mammalian type. He was led to conclude that "The tubercular process induced in the eyes of rabbits which have been subjected to the preven-

2. Löwenstein, E.: *Vorlesungen über Bakteriologie, Immunitätspezifische Diagnostik und Therapie der Tuberkulose*, Jena 1920, p. 213-267.

3. Römer, P.: *Tuberkulosevaccine*, in Kraus and Levaditi: *Handbuch der Immunitätsforschung, Ergänzungsband*, 1911, p. 310.

4. Baldwin, E. R., and Gardner, L. U.: *Reinfection in Tuberculosis. Experimental Arrested Tuberculosis and Subsequent Infections*, *Am. Rev. Tuberc.* **5**:429, 1921.

5. Trudeau, E. L.: *A Report of the Ultimate Results Obtained in Experimental Eye Tuberculosis by Tuberculin Treatment and Antitubercular Inoculation*, *Tr. Assn. Am. Phys.* **9**:168, 1894.

tive inoculation, differs in its course from that observed in the controls, and may even entirely abort, ending with almost complete restoration of the infected eyes, a result never observed in the controls." The results were not all that could be hoped for—Trudeau speaks of the immunity developed as "uncertain, imperfect and generally only relative"—but are noteworthy for Trudeau's keen observation that "in the prepared animals" in contrast to the unvaccinated controls "the introduction of infectious material in the eye gives rise almost at once to signs of violent and at first steadily increasing inflammation, which, however, in two to three weeks slowly begins to subside and may finally entirely disappear." It appeared to him that the more marked and immediate this inflammatory reaction, the better the prospect was for early abortion of the inoculation tuberculosis of the eye, and that a fair estimate of the degree of protection might be made according to the early appearance and intensity of this primary reaction. Trudeau was fully aware of the fact, to which attention is again being called in current literature on immunity in tuberculosis, that the same hypersensitiveness could be induced by the injection of dead tubercle bacilli; and he recognized this hypersensitiveness as a manifestation of resistance rather than the reverse, as he might have done in view of the acute inflammation developing in the reinoculated animal. Nevertheless, immunity did not seem to be developed in animals inoculated only with dead organisms, for, as he stated, "the introduction of living bacilli would appear necessary to the production of this relative immunity; the inoculation of merely chemical substances contained in the cultures is powerless to produce it. . . . Curiously enough, however, in animals which have been prepared with dead cultures the peculiar early reaction of the tissues to the virulent inoculation occurs to a certain extent; but the process goes on uninterruptedly to caseation and destruction of all the structures involved."

Later, Trudeau⁶ used as a vaccinating organism a culture of a human type tubercle bacillus isolated from the lung of a man dying from miliary tuberculosis, which lost its virulence in the first two years of culture. This culture (R_1), it may be remarked, is in extensive use today in many laboratories for the production of artificial immunity. In a typical experiment, he found that the injection of 0.25 mg. into the groin led within a month not only to a sufficiently heightened resistance to enable guinea-pigs to withstand 1.0 mg. of the same culture without harm, but also to survive from 115 days to a year after inoculation of a virulent culture which killed control animals in 55 days on the average. That this heightened resistance was again to be correlated

6. Trudeau, E. L.: Artificial Immunity in Experimental Tuberculosis, *Tr. Assn. Am. Phys.* **18**:97, 1903.

with a hypersensitiveness of the animals was shown by the report of his co-worker Hodenpyl on the histology of the lungs of the reinfected animals. These showed a tremendous reaction with much consolidation in protected animals during the first three weeks, and practical clearance at 110 days, with tiny nodules as a residue, encapsulated by polyhedral cells.

These experiments introduced a method which formed the basis of much subsequent research by Trudeau's pupils and their pupils in turn, including Baldwin, Krause, Soper, Paterson, Gardner, Long and others, as noted elsewhere in this article. In the same laboratory, Nichols⁷ repeated this work with results essentially similar to those obtained by Trudeau and Hodenpyl, noting especially the early outpouring of "epithelioid" cells in the vaccinated animals with rapid phagocytosis of the bacilli of the second injection, and a relatively sluggish process in the controls.

Other early experiments in which heightened resistance was developed by the use of living cultures were those of Hericourt and Richet (1888-1890)⁸ and de Schweinitz (1894).⁹ The latter vaccinated guinea-pigs with an avirulent culture of human type bacilli and the former vaccinated dogs with avian type bacilli and small doses of human type bacilli, concluding that in contrast to prevalent opinion "tuberculosis is a malady susceptible to vaccination." Neither set of experiments was extensive.

By selection, Arloing¹⁰ was able to obtain a tubercle bacillus able to multiply in the depths of bouillon, and much reduced in its capacity to form tubercles in animals. By further selection he claimed to have secured a race able to grow at 43 to 44 degrees. This was found to be still less pathogenic. By intravenous and subcutaneous injection as well as feeding this organism, he was able to increase the resistance of laboratory animals, goats and cattle to virulent infection. He estimated his success as follows: complete 50 per cent, relative 25 per cent, no success 25 per cent. Of his controls, 67 per cent showed extensive infection, 27 per cent some infection and 9 per cent none.

Löwenstein¹¹ injected tubercle bacilli subcutaneously into rabbits,

7. Nichols, J. L.: Studies on Immunity in Tuberculosis: A Histological Study of the Lesions of Immunized Rabbits, *Med. News*, Sept. 30, 1903.

8. Hericourt, J., and Richet, C.: Quelques nouveaux exemples de vaccination tuberculeuse chez le chien, *Compt. rend. Soc. de biol.* **46**:152, 1894.

9. De Schweinitz, E. A.: The Attenuated Bacillus Tuberculosis: Its Use in Producing Immunity to Tuberculosis in Guinea-Pigs, *Med. News* **65**:625, 1894.

10. Arloing, S.: Production expérimentale de variétés transmissibles du bacille de tuberculose et de vaccins antituberculeuse, *Compt. rend. Acad. d. sc.* **142**:1395, 1906; Vaccination antituberculeuse chez le beauf, *ibid.* **149**:962, 1909.

11. Löwenstein, E.: Tuberkulose-Immunität, in Kolle and Wassermann: *Handbuch der pathogene Mikroorganismen* **5**:660, 1913.

and then inoculated tubercle bacilli of the same strain into the anterior chamber of the eye. After the immediate inflammation was over, as in the case of Trudeau's animals, the infection was aborted, the eye returning to normal, while the same dose produced a progressive tuberculous iritis in controls.

VACCINATION OF CATTLE, 1900-1910

At the opening of the present century hope beat high for the development of a practical vaccinating method by which cattle could be rendered resistant if not immune to tuberculosis. Heightened resistance had been demonstrated repeatedly, and the avian bacillus and avirulent human type bacilli, while of low pathogenicity for mammals, had been found unquestionably to be effective in stimulating resistance to virulent organisms. Theobald Smith had distinguished the bovine type of bacillus as distinct from the human, Koch had accepted the distinction, and a number of investigators had found typical human type strains to be of low virulence for cattle. In later years, there was much dispute as to who originated the plan of vaccination of cattle with human type bacilli. The idea seems to have occurred to several men in several countries simultaneously. In reviewing several claims for priority, in 1907 Pearson¹² gives credit to M'Fadyean for the first experiments on the immunization of cattle against tuberculosis, and to Pearson and Gilliland for first proof by postmortem examination of the successful resistance of cattle vaccinated with human type bacilli against bovine infection rapidly fatal for nonvaccinated controls. To Behring he gives great credit for first proposing a practical method for the vaccination of cattle on a large scale.

M'Fadyean's first experiments¹³ were scanty and inconclusive but suggestive. Later, with several colleagues,¹⁴ he returned to them on a much greater scale, after the practical value of the procedure had been proved by others, making this interesting observation in experiments on the vaccination of healthy calves: In vaccinated animals the local lesion of reinfection soon became more or less sharply delimited and tended to develop as a round projecting tumor, whereas in the control the lesion persisted until a much later date, or until death, as a diffuse swelling. This limiting effect, which has been noted repeatedly in vaccinated animals of several species, will be discussed later.

12. Pearson, L.: A Review of Recent Investigations upon the Immunization of Animals against Tuberculosis, *Vet. J. London* **63**:101, 139, 1907.

13. M'Fadyean, J.: Experiments Regarding the Immunization of Cattle, *J. Comp. Path. & Therap.* **14**:136, 1901.

14. M'Fadyean, J.; Sheather, A. L.; Edwards, J. T., and Minett, F. C.: Experiments Regarding the Vaccination of Cattle Against Tuberculosis by the Intravenous Injection of Tubercle Bacilli of the Human and Avian Types, *J. Comp. Path. & Therap.* **26**:327, 1913.

Pearson and Gilliland,¹⁵ in the first large series of experiments of this type, found that repeated intravenous injections of tubercle bacilli from human sputum raised the resistance of young cattle to virulent bacilli of bovine origin to such a degree that they withstood without harm quantities of bovine cultures sufficient to cause death or extensive infection in cattle not similarly infected. Moreover, it was possible to inject without harm much larger quantities of the vaccinating organism than were required to produce this immunity. Pearson and Gilliland published a set of pictures of tuberculous organs in the controls and normal ones in the vaccinated, supporting their claims.

In 1902, Behring, Römer and Ruppel¹⁶ reported the first results of an extensive series of experiments carried out at Marburg. The work was undertaken originally in the effort to answer definitely these questions: (1) Are human type tubercle bacilli harmless for cattle, or, if they cause tuberculosis, is it different from that caused by the bovine type? and (2) Can cattle be immunized at will so that they will withstand a dose of tubercle bacilli fatal for nonimmunized controls? In the first series of experiments a bovine strain of low virulence was inoculated. The protocols for three of the animals are of particular interest. These cattle resisted repeated inoculations of a virulent strain of bovine type bacilli which killed control animals with generalized miliary tuberculosis in four weeks. The immunity set up was demonstrated in several ways, including resistance to repeated intravenous inoculation of virulent cultures, failure to contract tuberculosis on prolonged close contact with coughing tuberculous cattle, and finally by local resistance to tuberculous infection of the eye. Necropsy at the close of the experiment showed that infection did develop as a result of these repeated reinfections, but that it tended to spontaneous cure, the evidence persisting in the form of discrete nodules completely healed. It is noteworthy that the vaccinated animals used in these experiments gave positive tuberculin reactions, and at necropsy a year after the vaccination showed definite residues of the old vaccinating infection, often of considerable extent.

The Marburg experiment was continued by Römer,¹⁷ who later reported a great many more experiments in collaboration with others, which were of the same general type as those first described by Behring, Römer and Ruppel. An important observation was that not all strains of tubercle bacilli even of human origin were suitable for vaccination.

15. Pearson, L., and Gilliland, S. H.: Some Experiments upon the Immunization of Cattle Against Tuberculosis, *J. Comp. Med. & Vet. Arch.* **23**:673, 1902.

16. Behring, E.; Römer, P., and Ruppel, W. G.: Tuberkulose, *Beitr. z. exper. Path.* **5**:17, 1902.

17. Römer, P.: Neue Mitteilungen über Rindertuberkulose-bekämpfung, *Beitr. z. exper. Path.* **7**:77, 1904.

Occasionally human type bacilli set up an acute process in cattle. Finally, a method was evolved which was put into practice over large sections of Germany. Thousands of calves, first in several laboratories, and later on numerous estates, were inoculated with the Bovovaccin of Behring, Römer and their co-workers. Römer's directions called for the intravenous inoculation of a human type culture studied at the Marburg laboratory for years, marked by a particular firm and tested at the Marburg Institute. Calves were inoculated, preferably between the ages of 3 weeks and 4 months. However the method was applicable to cattle up to the age of 2 years, provided they were perfectly healthy and nonreacting to tuberculin. Two inoculations of the dried and later resuspended culture were given, 0.004 Gm. the first time and 0.02 Gm. the next.

It was several years before the value of the method could be determined. In the meantime, several similar attempts were in progress. Baumgarten¹⁸ renewed immunologic experiments begun nearly twenty years before. Stimulated by Behring's announcements, as he freely acknowledged, he was led to test the effect of single subcutaneous doses of human type tubercle bacilli on cattle. The experiments were successful in that the vaccinating infection was apparently harmless, and demonstrable resistance to bovine infection developed. The bacilli of the vaccinating injection did not seem to multiply to any great extent, most degenerating rapidly. Baumgarten hoped to be able to develop an antiserum which would protect against tuberculosis in the unvaccinated animal, but was unsuccessful. It is interesting that he expressed an opinion that just as human type bacilli seemed to be harmless but efficient protectors in cattle against bovine infection, so the reverse might be true in man, a speculation which has been raised several times since, without supporting evidence.

Independently of Behring, Koch and his associates were conducting similar experiments. Neufeld¹⁹ opened these in 1900 under Koch's direction. He found that it was possible by intravenous injection of living bacilli of the human type to immunize goats, asses and cattle against a surely fatal dose of virulent bovine type tubercle bacilli. Dead bacilli were unable to produce this immunity. As Koch was at that time presenting evidence to prove that tuberculin could immunize, Neufeld was careful not to push this line of reasoning far. In a later communication,²⁰ devoted largely to polemic with Behring, he reports

18. Baumgarten, P.: Ueber Immunisierungsversuchen gegen Tuberkulose, Berl. klin. Wchnschr. **41**:1124, 1904.

19. Neufeld, F.: Ueber Immunisierung gegen Tuberkulose, Deutsche med. Wchnschr. **29**:653, 1903.

20. Neufeld, F.: Zur Geschichte der Entdeckung der Immunisierung gegen Tuberkulose, Deutsche med. Wchnschr. **30**:660, 1241, 1904.

the continuation of these experiments, which reached their culmination in the announcement of a new immunizing method for cattle by Koch, Schütz, Neufeld and Miessner.²¹ In this it is repeatedly emphasized that the basis for the whole work is the difference established by Koch between human and bovine strains, a distinction for which Koch later acknowledged he was indebted originally to Theobald Smith. The method proposed by Koch and his associates does not differ greatly from that proposed about the same time by Behring and Römer. A single intravenous injection of 1 to 3 cc. of human type or spontaneously attenuated bovine type bacilli was found to confer complete immunity within three months against highly virulent bovine infection. The bacilli used were cultivated on glycerol broth and pressed free from the medium of growth between filter papers before emulsification in salt solution and injection.

In these experiments sudden rise in temperature on reinjection, with increased cough and other symptoms, was noted. The relation of this to immunity apparently was not grasped, and the phenomenon is described in particular in connection with a cow insufficiently immunized, which succumbed to the reinfection. As in the case of the Marburg method, the recommendations of Koch were given to the public in tentative fashion, in the certainty that only time and actual practical trial could tell whether the method had any value or not.

Investigators all over the world were not slow in putting the recommended procedure to test. The methods of Behring and Koch received an elaborate study at the hands of Weber and Titze,²² who tested cattle vaccinated by means of these methods, testing by intravenous and subcutaneous injection and inhalation and feeding of bovine tubercle bacilli, as well as by natural exposure in contaminated stalls. Heightened resistance, rather than immunity, was demonstrated but was definitely proved to be of short duration, two years at the most. A more serious defect by far, however, was found in the occasional establishment of human type tubercle bacillus infection in cows' udders, as a result of the vaccination. One such cow developed a chronic tuberculous mastitis from which tubercle bacilli continued to be discharged for a year and a half. Titze²³ went into this question as a special problem and found that following the vaccination tubercle bacilli were occasionally excreted in the milk in twenty-four hours. One cow began to excrete tubercle

21. Koch, R.; Schütz, W.; Neufeld, F., and Miessner, H.: Ueber die Immunisierung von Rinden gegen Tuberkulose, *Ztschr. f. Hyg.* **51**:300, 1905.

22. Weber, A., and Titze, C.: Die Immunisierung der Rinder gegen Tuberkulose, *Tuberk. Arb. a. d. k. Gsndhtsamte* **7**:1, 1907.

23. Titze, C.: Ausscheidung von Tuberkelbazillen mit der Kuhmilch nach intravenöser Injection menschlicher Tuberkelbazillen, *Tuberk. Arb. a. d. k. Gsndhtsamte* **9**:50, 1908.

bacilli in the third week and continued for 144 days. The unqualified conclusion was that "milk cows should not be immunized with living tubercle bacilli." Weber and Titze made the interesting observation that on feeding tubercle bacilli to their animals the vaccinated ones became sicker than the controls, unquestionably a manifestation of hypersensitiveness following alimentary absorption of tubercle bacilli.

In France, Vallee and Rossignol²⁴ presented the report of a commission which found that (1) a definite resistance could be demonstrated in animals vaccinated by Behring's method three months after the inoculation, but this disappeared within a few months; (2) the resistance of vaccinated subjects against natural contagion in close quarters with animals having open tuberculosis was not great and lasted only a few months.

In America, Theobald Smith²⁵ carried out tests for the Massachusetts Society for the Promotion of Agriculture, with no better success. He laid special emphasis on the great variation in the virulence of human strains for calves. By no means all were suitable for vaccination. One strain isolated from the lung of a man with pulmonary tuberculosis, a strain which was of low virulence for the rabbit and furthermore gave the reaction curve characteristic of the human type bacillus in glycerol broth, produced a violent, rapidly fatal tuberculosis in calves, with tuberculous pneumonia or tuberculous meningitis. There was also an especial tendency to attack the eyes. If animals survived first infection with this organism, however, they were able to withstand much larger doses. They could also be protected against this organism by vaccination with one of lower virulence. Smith noted, as had Behring, Koch, Weber and Titze and others, that "after an animal has been sensitized to tuberculin by an injection of living bacilli in the form of a vaccine, a second injection of vaccine calls forth an immediate febrile reaction as if tuberculin had been administered." Tuberculin sensitiveness in animals vaccinated with bacilli of low virulence for cattle persisted about a year.

In England, the Royal Commission on Tuberculosis secured results in essential agreement with the others proving the inadequacy as well as the dangers of the methods based on inoculation with human type bacilli. Griffith,²⁶ in reviewing the evidence some years later, states that it is "admitted generally now that injection of human tubercle bacilli for vaccination in milk cows is inadmissible on account of the

24. Vallee and Rossignol, cited by Calmette: *L'infection bacillaire et la tuberculose*, ed. 2, Paris, 1922, p. 592.

25. Smith, Theobald: *The Vaccination of Cattle against Tuberculosis*, J. M. Res. **18**:451, 1908; *The Vaccination of Cattle against Tuberculosis*, *ibid.* **25**:1, 1911.

26. Griffith, A. S.: *Human Tubercle Bacilli in the Milk of a Vaccinated Cow*, J. Path. & Bacteriol. **17**:323, 1913.

tendency of bacilli to pass out of the body with the milk." He quotes from his own experience the case of a cow which after receiving 150 mg. of human type tubercle bacilli commenced to discharge them in her milk twenty-four hours later, and continued to do so until "dried off" forty-four days afterward. Five and a half months later, pus containing tubercle bacilli was obtained from two of the quarters of the udder. This condition continued until the five hundred and twenty-ninth day, when the cow was killed. Bacilli isolated from the udder were shown by cultivation and rabbit test to be of the human type. In other experiments human type bacilli were injected subcutaneously into eleven heifers and in seven identified shortly afterward in the fluid obtained on irrigation of the ducts with saline.

Other investigators in Germany, Hungary, Denmark, Sweden and Italy secured results of the same general trend. Zwick and Titze²⁷ and Hutyra²⁸ have reviewed the results obtained. In general, the experience in vaccination of cattle from 1900 to 1910 may be summarized as follows: 1. An increase in resistance to reinfection is unquestionably conferred by vaccination of cattle with human type tubercle bacilli. 2. This is on the average of only a year's duration. 3. There is grave danger of infecting the udder, so that the milk may contain tubercle bacilli. 4. In general, human type bacilli are of low virulence for cattle, but this is not always the case, some strains causing serious disease.

EXPERIMENTS OF RÖMER ON IMMUNIZATION AND APPLICATIONS MADE TO HUMAN TUBERCULOSIS

Empiricism ruled the cattle experiments of 1900 to 1910. Heightened resistance was sought, and this goal loomed larger in men's minds than the mechanism by which it was reached. No serious attempt was made to explain how the partial immunity was developed, before the experiments of Römer, who in collaboration with Joseph carried out a long investigation convincing by the sheer monotony of the positive results secured. He²⁹ opened the series with an article entitled "Specific Hypersensitiveness and Immunity to Tuberculosis," with an extensive review of the literature on tuberculin and earlier experiments on immunity in already infected animals. With reference to the latter, illustrating his point with temperature charts, he says "In all curves we see the same phenomenon; in the immunized animal a rapid, violent

27. Zwick, W., and Titze, C.: Die Schützimpfung gegen die Rindertuberkulose, in Kolle and Wassermann: Handbuch der pathogenen Mikroorganismen 5:719, 1913.

28. Hutyra, F.: Hutyra-Marek, Spezielle Pathologie und Therapie der Haustiere, ed. 6, Jena, 1922, p. 687.

29. Römer, P.: Spezifische Ueberempfindlichkeit und Tuberkuloseimmunität, Beitr. z. klin. Tuberk. 11:79, 1908.

reaction ending in healing, in the controls typically gradual development of the infectious process, which finally leads to death." He goes on to state, "I am inclined to see in this hypersensitiveness not a mere symptom coincidental with immunity, but the actual cause or at least one of the causes of the artificial immunity."

He then quotes the first accurate observation recorded on hypersensitiveness in tuberculosis in relation to immunity, the first description of what later became known as the Koch phenomenon, the full significance of which the discoverer himself had failed fully to grasp. Koch³⁰ wrote in 1891: "If a healthy guinea-pig be inoculated with a pure culture of bacilli, the wound ordinarily closes and appears to heal from the beginning. But toward the tenth or fifteenth day there appears at the point of inoculation a hard nodule which soon opens spontaneously to produce an ulcer which persists until the death of the animal. On the other hand, guinea-pigs which have been infected from four to six weeks beforehand and inoculated anew, behave very differently. No nodule forms at the point of inoculation, but from the next day or second day this point becomes indurated and takes on a color at first violet red, and then blackish, over an area from 0.5 to 1 cm. in width. During the succeeding days the skin becomes necrotic. It soon sloughs and leaves behind it a superficial ulceration which heals rapidly and definitely, without swelling of the regional lymph nodes. Thus the inoculated tubercle bacilli act quite differently under the skin of a guinea-pig already tuberculous, and under that of a normal animal."

Römer³¹ proved beyond question that even the highly susceptible guinea-pig could be immunized against doses of virulent tubercle bacilli surely fatal for controls. To produce this immunity, however, it was necessary to infect the guinea-pigs. Animals vaccinated with dead or avirulent bacilli behaved exactly like controls with respect to reinfection, while truly tuberculous pigs were fully immune to small reinfections and highly resistant to large. In fact, as Römer³⁰ had brought out before, the immunity to reinfection was the higher the more virulent the vaccinating virus. The dilemma which Römer thus clearly and concisely exposed is at once apparent. A vaccinating infection sufficiently powerful to make the resistance of an animal perfect to massive superinfection from outside, of itself sets up progressive disease.

Through the large number of controls used Römer was able to distinguish clearly the effects of the vaccinating infection and superinfection by the extent of the lesions and the condition of tissue at the site of

30. Koch, R.: Fortsetzung der Mitteilungen über ein Heilmittel gegen Tuberkulose, *Deutsche med. Wchnschr.* **17**:101, 1891.

31. Römer, P.: Weitere Versuche über Immunität gegen Tuberkulose, durch Tuberkulose, zugleich ein Beitrag zur Phthisiogenese, *Beitr. z. klin. Tuberk.* **13**:1, 1909.

reinoculation. When the reinfection was kept below certain limits the reinfected animals never showed more extensive tuberculosis than the vaccinated but not reinfected pigs, and regularly showed less than the nonvaccinated pigs, which received the same virulent dose. In the vaccinated animals the skin and regional lymph nodes at the site of reinfection finally showed healed lesions, whereas in the nonvaccinated the lesions remained active at the same site of inoculation.

The series of animals studied was large enough to include a laboratory rarity, guinea-pigs with spontaneous tuberculosis, the infection being detectable through the tuberculin test and presence of enlarged cervical lymph nodes. Like the artificially infected pigs, these were resistant to reinfection.

In conjunction with Joseph, Römer³² made an exact study of the degree of immunity attainable by artificial infection. After vaccinating with a weakly virulent human strain of bacilli, he reinjected $\frac{1}{4,000,000}$ mg. of highly virulent bovine type bacilli intracutaneously without setting up a progressive infection. One one hundred thousandth of a milligram was too much for the vaccinated animals to withstand, although the process set up by this amount was less extensive than that in the nonprotected controls.

In other experiments Römer and Joseph first infected guinea-pigs with $\frac{1}{100,000}$ mg., and after local signs of infection had developed removed a tuberculous regional lymph node, emulsified it and injected portions into the same animal again and into normal animals. The normal animals developed progressive tuberculosis while the previously infected animals were resistant.

Sheep also were made more resistant by a light primary infection. Animals protected by the injection of $\frac{1}{10}$ mg. of tubercle bacilli, from eight to ten months later resisted the inoculation of $\frac{2}{10}$ mg. perfectly, showing no more tuberculosis finally than animals not reinfected. But $\frac{2}{10}$ mg. was sufficient to cause progressive, generalized, fatal tuberculosis in nonvaccinated controls.

In the course of his investigation, Römer called attention not only to the resistance to superinfection, but also to the changed anatomic type of tuberculosis in the superinfected animal. Ulcerative tuberculosis of the lungs developed in the superinfected animals in contrast to the simple caseonodular type in the primarily infected pigs. This was to be considered a pulmonary manifestation of the Koch phenomenon, and appeared to Römer to be of great significance in explaining the nature of ulcerative tuberculosis or common phthisis in man. To Römer,³³ and to others, ulcerative tuberculosis of the lungs meant not only superinfec-

32. Römer, P., and Joseph, K.: Die tuberkulose Reinfektion, Beitr. z. klin. Tuberk. 17:287, 1910.

33. Römer, P.: Kindheitsinfektion und Schwindsuchtsproblem im Lichte der Immunitätswissenschaft, Tuberculosis 9:129, 1910.

tion but massive superinfection, whether as a reinfection from within or from without. Hamburger³⁴ put it thus, "Tuberculosis takes on the form which we call phthisis, because it is a tuberculous process developing in an organism already tuberculous."

It was at this period of tuberculosis investigation that it was becoming clear for the first time that tuberculosis was not a disease confined chiefly to adults. Endemiologic studies with tuberculin had just shown the enormous extent of childhood infection. Clinical tuberculosis was of vastly less extent, and Römer³⁵ promptly interpreted these newly appreciated facts in the light of his experiments on immunity. Childhood infection, he was led to believe, usually of mild character, operated just as did his light vaccinating infections. Mild superinfections, which must almost inevitably occur in the course of ordinary existence, were aborted, as were the light artificial superinfections in his guinea-pigs. Clinical tuberculosis, however, developed when superinfection, whether from within or without, overwhelmed the artificially heightened resistance. When this occurred, however, tuberculosis took on the characteristic anatomic type of phthisis. Phthisis meant massive reinfection, and Römer committed himself to the belief that massive reinfections came from within. Hamburger³⁴ also spoke of pulmonary "tuberculosis of adults as almost always a recurrent tuberculosis."

Since Römer's time, the doctrine of an adult immunity due to tuberculous infection in early life has become so widely accepted that in the natural effort of students to simplify what at the best is a highly complex matter other factors have been largely ignored. At the same time, the impression has become firmly implanted that children are less resistant to tuberculosis than adults because less well immunized by infection. Krause³⁶ has pointed out numerous fallacies in the line of reasoning involved, clearly showing that infection-immunity in the child may well be higher than in the adult. A number of other factors, of which anatomic difference in the lymph system is one of the most important (see also Krause³⁶), however, favor that spread which is looked on as a low resistance in the child. The allergic or hypersensitive state, which Römer so definitely correlated with resistance, may be and usually is more marked in children than in adults, because of the shorter interval since the infection establishing the allergy. Krause believes that if we

34. Hamburger, F.: Die Tuberkulose als Kinderkrankheit, München. med. Wehnschr. **55**:2702, 1908.

35. Krause, A. K.: Human Resistance to Tuberculosis at Various Ages of Life, *Am. Rev. Tuberc.* **11**:303, 1925.

36. Krause, A. K.: Experimental Studies on Tuberculous Infection, *Am. Rev. Tuberc.* **6**:1, 1922.

conceive of resistance to tuberculosis as a composite of two bodily forces, lymphatically the generality of children are less resistant than adults, while allergically they are more resistant. And to their higher allergic reactive capacity toward metastasizing infection, he attributes much of the ability of the child to withstand the common widely disseminated metastatic tuberculosis of childhood. It would lead too far afield to discuss this plausible line of argument further. The present review is concerned only with that phase of heightened resistance which is the result of infection, with full recognition of the fact that other mechanisms concur in raising resistance as age increases.

RECENT ATTEMPTS TO PRODUCE A PRACTICAL METHOD OF VACCINATION

Among numerous efforts directed toward the vaccination of cattle between 1900 and 1910 were studies of Calmette and Guérin. These began as an outgrowth of Calmette's views on the intestinal origin of pulmonary tuberculosis. Calmette and Guérin³⁷ found that animals could be vaccinated by alimentary administration of tubercle bacilli, and made to develop the characteristic evidence of infection, sensitiveness to tuberculin. This gradually waned, but subsequently these animals were able to withstand larger doses of virulent bacilli, which again caused the tuberculin reaction to become positive. The infection thus set up, however, tended to subside, as shown by the ultimate return to nonsensitiveness to tuberculin. In 1908, a study³⁸ was commenced which is in its most active stage today. Interested first in the intestinal absorption of tubercle bacilli, they were led to study the effect of bile on tubercle bacilli. They found potato impregnated with glycerolated bile to be a good medium for the growth of the bacillus. But in the course of several generations on beef bile mediums, a profound physiologic change occurred. Bovine type bacilli cultivated on this medium lost their capacity to produce tubercles in cattle, although retaining for a time their full pathogenicity for guinea-pigs. Injected into cattle they did, however, arouse a general febrile reaction, which the authors speak of as a "typho-bacillosis."

Early experiments³⁹ indicated that a type of immunity could be created in cattle by treatment with this bacillus. If from eight months to a year after vaccination with the "biliated" organism calves received

37. Calmette, A., and Guérin, C.: Contribution à l'étude de la vaccination des bovidés contre la tuberculose par les voies digestives, *Ann. de l'Inst. Pasteur* **21**:525, 1907.

38. Calmette, A., and Guérin, C.: Sur quelques propriétés du bacille tuberculeux cultivé sur la bile, *Compt. rend. Acad. d. sc.* **147**:1456, 1908.

39. Calmette, A., and Guérin, C.: Nouvelle contribution à l'étude de la vaccination des bovidés contre la tuberculose, *Ann. de l'Inst. Pasteur* **22**:689, 1908.

intravenously a dose of virulent tubercle bacilli fatal for untreated mates, a prompt febrile reaction occurred, followed by perfect recovery. If such animals were killed six or eight months later, virulent tubercle bacilli, as shown by guinea-pig inoculation, could still be found in their bronchial and mediastinal lymph nodes. These bacilli during life set up no tubercle and manifested their presence in no way, not even by arousing sensitiveness to tuberculin. Yet many months after the virulent inoculation, tuberculosis might apparently arise from their presence, as in several instances described, an event which Calmette and Guérin interpreted as a waning of the resistance conferred by the biliated bacilli.

In later generations on the bile mediums the bovine type tubercle bacillus lost its virulence for guinea-pigs. In the fifteenth generation, the authors⁴⁰ found 1 mg. to be nonfatal for the guinea-pig, while 100 mg. did not kill a calf; whereas 5 mg. had led to a fatal issue within thirty days, before cultivation on bile mediums was commenced. A calf vaccinated in 1908 with successive 5 mg. doses, in 1909 withstood 200 mg. at one dose and 380 mg. altogether. It was noted that in this animal agglutinins for the tubercle bacillus were present, but complement-fixing bodies were not. In later experiments,⁴¹ it was found that the serum of cattle immunized by the action of biliated bacilli had no protective or curative action in other animals; on the other hand, it seemed to favor in some way the elimination of tubercle bacilli in the bile of infected animals. Vaccination of animals with biliated organisms appeared to have the same effect, and at this stage of their experiments Calmette and Guérin believed that the immunizing action of vaccination was due in large measure to this effect on elimination.

Later experiments⁴² added to the evidence for this theory. Cattle vaccinated with biliated bacilli withstood without illness doses of virulent bacilli which killed controls in four or five weeks. Little by little the virulent organisms were expelled from the vaccinated calves with the dejections. Up to eighteen months, however, they could still be found in the lymph nodes, with all of their original virulence for guinea-pigs preserved, but causing no anatomic lesion in the nodes of the vaccinated animal. An experiment is described in which eight 9 month old calves

40. Calmette, A., and Guérin, C.: Sur quelques propriétés du bacille tuberculeux d'origine bovine, cultivé sur bile de boeuf glycinée, *Compt. rend. Acad. d. sc.* **149**:716, 1909.

41. Calmette, A., and Guérin, C.: Recherches expérimentales sur la défense de l'organisme contre l'infection tuberculeuse (serotherapie-immunité), *Ann. de l'Inst. Pasteur* **25**:625, 1911.

42. Calmette, A., and Guérin, C.: Nouvelles recherches expérimentales sur la vaccination des bovidés contre la tuberculose, et sur le sort des bacilles tuberculeux dans l'organisme des vaccinés, *Ann. de l'Inst. Pasteur* **27**:162, 1913.

free from tuberculosis, as determined by the tuberculin test, received two vaccinating inoculations of biliated bovine type tubercle bacilli in their thirty-third and thirty-fourth generation on bile mediums. One month after the second inoculation the calves received 3 mg. of a virulent strain. A control died thirty-four days later with massive tuberculosis. The vaccinated animals, killed at intervals from the first to the eighteenth month, showed no lesions. Yet in every case virulent tubercle bacilli, capable of setting up generalized fatal tuberculosis in the guinea-pig, were recovered from the lymph nodes.

This extraordinary tolerance of the vaccinated animal for virulent tubercle bacilli is difficult to explain in terms of any theory of immunity to tuberculosis. Calmette,⁴³ referring to the situation in animals refractory by nature to human type tubercle bacilli, in which the bacilli remain in the body fluids or tissues like harmless foreign bodies, speaks of toleration by the host without the power of destruction, but never with the establishment of a symbiosis between bacilli and cells which take them in. And further "it is a tolerance of this sort which artificial immunization should aim to produce." But in the light of all other trustworthy experiments since the time of Römer, we know that the active immunity which results from infection establishes an intolerance, manifested by an explosive reaction of the Koch phenomenon type. If the failure of symbiosis between the superinfecting bacilli and the body cells, together with the elimination of these bacilli by such channels as the bile and milk, as Calmette describes in his earlier works, be accepted as an equivalent for the Koch phenomenon, we have the reconciliation. But it is difficult to see the connection, and yet others have noted this same extraordinary tolerance. As will be brought out later, we have a working histologic basis to explain an immunity of the Koch phenomenon type, which is lacking in the first explanations of immunity induced by primary inoculation with biliated bacilli.

Later (1920), Calmette and Guérin⁴⁴ described the resistance of cattle to natural contagion in association with infected cattle. Six cattle vaccinated with 20 mg. of bacilli in their seventieth transfer in bile and four nonvaccinated controls were exposed to contamination in the same stall for two years. At the end of this time three of the controls reacted positively to tuberculin. One control remained free from tuberculosis. Of the vaccinated animals, three which had been vaccinated only once developed infection after two years. The others, vaccinated again at the end of the first year, remained free from tuberculosis.

43. Calmette, A.: *Tubercle Bacillus Infection in Man and Animals*, trans. by Soper and Smith, Baltimore, 1923, p. 571, ff.

44. Calmette, A., and Guérin, C.: *Nouvelles recherches expérimentales sur la vaccination des bovidés contre la tuberculose*, *Ann. de l'Inst. Pasteur* 34:553, 1920.

In a later publication,⁴⁵ they take up the tuberculin reaction in a somewhat different light than previously. Referring back to their article of 1920, they state that they were struck by the brief duration during which the tuberculin reaction was positive. Apparently, immunity lasted no longer than sensitiveness, which they believed coincided with the length of time during which tubercle bacilli persisted in the body. Previously they had published protocols demonstrating immunity in animals vaccinated but not reacting to tuberculin, and had used the negative tuberculin reaction following reinfection as evidence of the failure of that infection to take hold. With a manifestly changed point of view in 1924, they tried to prolong a period of tuberculin hypersensitiveness (which was negligible or nonexistent in the animals described in protocols of previous years), on the ground that "a positive tuberculin reaction is no longer to be considered evidence of infection. It is, in cattle as well as in man, an evidence of immunity. It only reveals the existence somewhere in the reacting organism of a focus, active or latent, recent or old, of symbiosis with a bacillus, virulent or nonvirulent, with lymphocyte, macrophage or giant cell." The authors go on to state that animals inoculated with avirulent tubercle bacilli will react in the same manner as infected ones. For the production and maintenance of this desired state of tuberculin sensitiveness, they now find that subcutaneous inoculation is better than intravenous. Elimination following subcutaneous inoculation is prolonged, and as long as living bacilli persist in symbiotic existence with body cells, sensitiveness remains. As long as this persists the phenomenon of Koch, protective in its effect, occurs on reinoculation. This is entirely in harmony with views expressed years before by Römer.

The chief difference between the theories of Calmette and those of Römer and, in more recent years, Krause, is with regard to the mechanism of the vaccination. Römer had regarded the immunizing power of an infecting organism as proportional to its virulence. Krause has repeatedly insisted on the necessity of anatomic tubercle for the production of increased resistance to further infection. In commenting on Calmette's method of vaccination, Krause⁴⁶ has said that "it differed from all of the many other modified strains of tubercle bacilli in one decisive particular. This was that while the materials of Richet and Hericourt, Behring, Koch, Theobald Smith, Webb and Williams, etc., conferred protection as they gave rise to tubercle formation in the animal under immunization, Calmette's BCG raised resistance yet without set-

45. Calmette, A., and Guérin, C.: Vaccination des bovidés contre la tuberculose et methode nouvelle de prophylaxie de la tuberculose bovine, *Ann. de l'Inst. Pasteur* **38**:371, 1924.

46. Krause, A. K.: Calmette's Protective Inoculation against Tuberculosis, editorial, *Am. Rev. Tuberc.* **10**:219, 1924.

ting up anatomic change. Every student of tuberculosis will at once appreciate the enormous importance of the difference." The factors considered by Krause to be essential in the establishment of resistance will be considered later.

The protocols of the 1924 article, however, read much more like those of previous investigators. The vaccination with BCG, as Calmette and Guérin term the biliated bacillus, does set up an anatomic lesion at the site of the subcutaneous inoculation, which slowly subsides, disappearing between the tenth and eighteenth month; and for from six to twelve months the tuberculin reaction is positive. The lesion is described in an animal dying of intercurrent disease twenty-five days after vaccination, as fibrous, lardaceous, partly necrotic, containing tubercle bacilli, and resembling somewhat an old lymphnodal tuberculosis. On reinoculation with virulent bacilli there is always an immediate and violent febrile reaction, reaching a maximum in from nine to twelve hours after injection, but the animals recover and do not develop progressive tuberculosis as do the nonvaccinated controls receiving the same dose of virulent bacilli. In the reinoculated animals at necropsy the lymph nodes do not contain virulent tubercle bacilli with the uniformity recorded in previous experiments.

Whatever may be said of the apparent contradiction in the old and the recent articles of Calmette and Guérin, and the nature of the immunity aroused, empirically the results are more impressive than any others recorded in this field of investigation. If we may take the reports of the authors at their face value, vaccinating inoculation is almost absolutely innocuous, and the lesions of reinfection are far less serious than those described after other types of vaccination with living bacilli. However, as Krause⁴⁶ wisely points out, "No one who is at all familiar with the literature of the past on preventive inoculation against tuberculosis, will rush in to render a final opinion on the efficacy and practicability of any new method until this method has had trial in many hands, in many lands, in many subjects. One thinks at once of the thousands and tens of thousands of cattle which had to be employed and closely followed for a decade and more before a proper balance could be struck on the value of preventive inoculations devised by men who are among our great names—Behring, Koch, Smith, Vallee. And there can be no doubt that until Calmette's methods have had similar scrutiny the merits of his BCG must remain *sub judice*."

Calmette's method has not been confined to the vaccination of cattle. Perfect success has been claimed in the vaccination of anthropoids in their natural environment by Wilbert,⁴⁷ and a spectacular experiment on

47. Wilbert, J.: Expériences de vaccination des singes contre la tuberculose par le BCG, Ann. de l'Inst. Pasteur 39:641, 1925.

human beings is in progress in France.⁴⁸ In the last extensive report available it is recorded that from July 1, 1924, to June 1, 1925, 2,070 new-born children have been vaccinated. These were from families or an environment in which open tuberculosis close at hand rendered early natural infection seemingly inevitable. Vaccination was by ingestion. Many experiments on laboratory animals had indicated the practicability of this route.⁴⁹ One centigram of living culture was emulsified in glycerol, glucose and water and taken in three doses on the fourth, sixth and eighth, or fifth, seventh and ninth days after birth. The records for 423 children for six months after vaccination have been made available. One hundred and thirty-seven, or 32.6 per cent, of these have been exposed to familial contagion. In not one of these has death from tuberculosis occurred. Thirty have died from other causes, with the existence of tuberculosis not suspected. Figures compiled by the authors indicate that the mortality from tuberculosis under the same conditions without vaccination was 24 per cent for the three year period from 1922 to 1925. Trial of the method in human beings has thus been encouraging at the start, and more cannot be said at the present time.

Vaccination of children with living tubercle bacilli to many has seemed in theory entirely logical, although few have been willing to risk the responsibility. As Pearson and Gilliland said twenty years ago, the whole story of immunization has led investigators to expect a solution of tuberculosis immunity through the use of a living virus. Moreover, most children do become infected with living tubercle bacilli. Thousands of postmortem observations have made this fact unescapable. We have abundant reason for believing, further, that such infections have operated only to stimulate resistance against further infection. The dosage of bacilli which led to these infections was absolutely uncontrolled. It is only natural to feel that the same thing might be accomplished, without the danger of exceeding a dose which a child could handle, by introducing accurately counted small doses of bacilli.

Prior to the experiments of Calmette, however, attempts to vaccinate children with living true tubercle bacilli had rarely been made, and only one important set of records is available. Living tubercle bacilli have frequently been injected by way of therapy into human beings already suffering from tuberculosis, but therapy is outside of the scope of this article. Webb and Williams inoculated the children of tuberculous

48. Calmette, A.; Guérin, C., Weill-Halle and others: *Essais d'immunisation contre l'infection tuberculeuse*, Presse méd. **32**: III, 553, 1924. *Essai de premunition par le BCG contre l'infection tuberculeuse de l'homme et des animaux*, *ibid.* **33**: II, 825, 1925.

49. Calmette, A.; Negre, L., and Boquet, A.: *Essais de vaccination du lapin et du cobaye contre l'infection tuberculeuse*, *Ann. de l'Inst. Pasteur* **36**:625, 1922.

parents with increasing numbers of bacilli, using a method previously found practical in guinea-pigs. Using the method of Barber for the isolation and injection of single bacilli, they⁵⁰ had found it possible to inject virulent tubercle bacilli in increasing doses until the total injected was enormous. In a typical experiment, pigs received tubercle bacilli as follows: first day, 5 bacilli; fourth day, 15; ninth day, 50; eighteenth day, 150; twenty-ninth day, 250; thirty-seventh day, 500; sixty-eighth day, 700, and finally up to a total of 3,000 bacilli. On killing such animals no tuberculosis was found. Yet 150 bacilli of this strain at a single first dose caused generalized tuberculosis in controls.

Later, one guinea-pig received in the course of nine months 141,835 living virulent tubercle bacilli.⁵¹ At the end of this time the animal was killed. No tuberculosis was found in any organ. More remarkable than this, however, is the fact that the animal two months before death, after receiving 42,235 bacilli, did not react to tuberculin. The general health was good, an increase in weight of 200 Gm. occurring in the course of the experiment. Later, similar results were obtained with monkeys.⁵² "Two monkeys each received safely enough virulent tubercle bacilli to kill 12,000 full grown guinea-pigs." One monkey received doses from 1 bacillus to 65,000 in the course of eight months, and at necropsy showed no tuberculosis. Tubercle bacilli could not be found in the organs by smear or inoculation.

Others stimulated by this apparent success to repeat the experiments, failed to secure as good results. Bruyant⁵³ found it impossible to prevent the development of tuberculosis by this means, although lesions anatomically characteristic of resistance developed. Brown, Heise and Petroff⁵⁴ found that after repeated doses of virulent tubercle bacilli animals outlived controls infected only once. All animals thus infected, however, developed tuberculosis; and although they lived a year on the average and died of intercurrent infection, whereas the controls lived only from 91 to 116 days, the authors believed the tuberculosis set up was sufficiently generalized ultimately to prove fatal.

50. Webb, G. B., and Williams, W. W.: Immunity Production by Inoculation of Increasing Numbers of Bacteria Beginning with One Living Organism, *J. M. Res.* **20**:1, 1909.

51. Webb, G. B., and Williams, W. W.: Immunity in Tuberculosis. A Further Report on Its Production by the Inoculation of Increasing Numbers of Bacilli, *J. M. Res.* **24**:1, 1911.

52. Webb, G. B., and Williams, W. W.: Immunity in Tuberculosis. Its Production in Monkeys and Children, *J. A. M. A.* **57**:1431, 1911.

53. Bruyant, L.: Effets des inoculations de doses faibles et répétées de bacilles tuberculeux chez le cobaye, *Compt. rend. Soc. de biol.* **71**:143, 1911.

54. Brown, L.: Heise, F. H., and Petroff, S. A.: An Attempt to Immunize Guinea-Pigs by the Use of Graduated, Repeated Doses of Living Tubercle Bacilli, *J. M. Res.* **30**:475, 1914.

The results obtained by Webb and Williams were so good, however, as to encourage them ⁵² to attempt the immunization of children. Two boys, one 3 years and the other 3 months old, sons of tuberculous parents, both therefore likely to contract tuberculosis in the course of natural events, were inoculated with living tubercle bacilli at weekly intervals, in the following doses: 1, 3, 5, 8, 12, 18, 25, 35, 50, 75, 100, 125, and 150 bacilli. The children were negative to the Pirquet test at the start and remained so. Webb and Gilbert ⁵⁵ later reported on a child which at seven day intervals received 2, 3, 5, 7, 10 and 12 bacilli. The Pirquet reaction was questionable or negative at the start. Six weeks after the first injection, a small nodule formed at the site of inoculation, and ten days later two others appeared, one on the same arm and one on the opposite. All three were removed under general anesthesia. Sections showed numerous tubercle bacilli. Later the axillary lymph nodes on one side became involved and were removed. No further change occurred, and some months after these events the child was in perfect health. The Pirquet reaction, however, was now positive. No further details are recorded.

One other experiment on primary inoculation of nontuberculous children with live tubercle bacilli is on record. Selter ⁵⁶ has published a detailed account of the vaccination of nine children. He inoculated doses of virulent human type bacilli ranging from 12 bacilli to 10,000. He is unconvinced by Calmette's results, on the ground that Calmette's vaccine does not produce anatomic tubercle, and in children has not led to the development of a positive tuberculin reaction, both of which to Selter are necessary for the development of immunity.⁵⁷ With the larger doses of living bacilli Selter produced subcutaneous nodules which in some instances broke down and discharged to the surface. Small doses did not produce visible nodules, but in eight of the nine children, all of whom were tuberculin-negative at the start, tuberculin sensitiveness developed. In one child 50 bacilli apparently failed to infect. Aside from the production of the nodules, the vaccination seemed harmless. General health was not impaired, nor did the regional lymph nodes appear to be involved. One child died of pneumonia three months after inoculation. No tuberculous changes were noted at necropsy except a small ulcerated nodule of tuberculous granulation at the site of inoculation. Emulsions of the internal organs failed to infect

55. Webb, G. B., and Gilbert, G. B.: Immunity in Tuberculosis. Further Experiments, *J. A. M. A.* **63**:1098, 1914.

56. Selter, H.: Ein Versuch zur Tuberkuloseschutzimpfung des Menschen, *Deutsche med. Wchnschr.* **51**:1181, 1925.

57. Selter, H.: Ist eine Schutzimpfung des Menschen gegen Tuberkulose mit abgetöteten oder avirulenten Tuberkelbazillen möglich? *Deutsche med. Wchnschr.* **50**:1825, 1924.

guinea-pigs, but tubercle bacilli were detected in the regional lymph nodes by this method. The other children passed through acute infections without any spread of their inoculation tuberculosis. Selter was unable at the time of publication to draw any conclusions as to immunity conferred, but feels that the procedure, while not to be recommended for general application, is possibly justifiable in the case of children exposed in the home to massive infection.

Selter's trial on children is the continuation of extensive investigation on laboratory animals.⁵⁸ These in general plan and results resemble the experiments of Römer and need not be reviewed in detail here. The conclusion was that immunity could be conferred only by the use of living bacilli and the production of actual tuberculous lesions, accompanied in turn by tuberculin sensitiveness. Latent or chronic mild tuberculosis was found to confer complete immunity to small doses of virulent bacilli. Larger reinfections were met by a strong response which localized the reinfection to the site of inoculation. If the first inoculation did not lead to true infection, reinfection led to generalized tuberculosis exactly as in nonvaccinated controls.

Selter used for his vaccinating inoculation a mixture of living, intact bacilli and supposedly living bacillary protoplasm from ground bacilli. In the preparation of this material, which he designates "vital tuberculin," a mass of moist bacilli from an old culture is rubbed up in an agate mortar until only 0.001 per cent of the bacilli remain intact. The ground protoplasm of the rest is believed to act as "aggressin," favoring the action of the bacilli present, too few by themselves to set up infection. At the same time hypersensitiveness is rapidly stimulated. Experiments on cattle are in progress, in which the same method of inoculation is used. It is too early yet to form any conclusion as to the success of this experiment.

Other experiments in progress on the immunization of cattle are those of Baumgarten and Uhlenhuth. Not deterred by the disappointing results of cattle inoculation in 1900 to 1910, Baumgarten⁵⁹ has continued the use of a subcutaneous inoculation of human type bacilli sufficiently virulent to produce a tuberculous nodule. The dose recom-

58. Selter, H.: Die Immunitätsverhältnisse bei Meerschweinschentuberkulose, *Ztschr. f. Hyg.* **95**:159, 1922; Weitere Untersuchungen über künstliche Tuberkuloseimmunisierung, *ibid.* **98**:192, 1922. Selter, H., and Knauer: Vorversuche für eine Rindertuberkulose-Schutzimpfungs-Verfahren, *Ztschr. f. Infektionskr.* **24**:291, 1923. Selter, Knauer and Geschke: Zum Problem der Tuberkulose-Schutzimpfung, *München. med. Wchnschr.* **70**:1499, 1923. Selter, H.: Die Tuberkuloseimmunität auf Grund der heutigen Kenntnisse, *Beitr. z. klin. Tuberk.* **55**:318, 1923.

59. Baumgarten, P.: Das Tübinger Schutzimpfungsverfahren gegen Rindertuberkulose und seine Wirksamkeit in der Praxis, *Beitr. z. path. Anat. u. allg. Pathol.* **63**:259, 1917.

mended is 1 cg.; the nodule that forms is well localized and retrogresses after a time, but immunity permits four years or more, according to his claim. One animal in the course of four years after vaccination received seven inoculations of virulent bovine type bacilli in dosage sufficient to kill controls. Increased resistance toward infection is demonstrable two and one half months after vaccination and reaches its maximum after nine months. For best results, calves 3 months old should be inoculated. Once spontaneous infection has occurred, vaccination is of no value. The number of animals used in the experiment is small.

Uhlenhuth⁶⁰ attempted at first to immunize animals by massive injections of dead bacilli, but animals so vaccinated succumbed to generalized tuberculosis on infection with virulent bacilli exactly as did nonvaccinated controls. Living bacilli injected intraperitoneally as a vaccinating measure led to much better but not invariably successful results. A severe febrile reaction occurred on reinfection, followed in most instances by good recovery and continuance in health. On the whole, Uhlenhuth feels that the immunization of cattle is difficult.

The experiments of Baumgarten and Uhlenhuth have been carried out on only a small number of animals, and seem to be a continuance of, rather than an advance over, the hundreds of similar tests carried out as a sequel to the first attempts by Behring and Koch to secure a practical method of vaccinating cattle on a large scale.

The literature cited up to this point in no way exhausts the list of attempts to furnish a basis for large scale vaccination in either cattle or man. Experiments such as those of Haupt⁶¹ who is continuing the use of Klimmer's vaccine first proposed in 1908, can merely be mentioned. Klimmer believed he had modified the virulence of human type bacilli by passage through other animals until avirulent for man, although still immunizing in action. Haupt reviews the literature on the Klimmer method and reports recent success in cattle. Shiga⁶² has attempted to reduce the virulence of tubercle bacilli by adapting them to growth in the presence of acriflavine. Guinea-pigs vaccinated with these bacilli lived months longer than controls, following reinfection. Another group of Japanese are engaged in the modification of virulence of tubercle bacilli by growth on mediums containing saponin. The resultant organisms are of greatly reduced virulence but are said to retain the

60. Uhlenhuth, P.: Experimentelle Untersuchungen zur Frage der Immunität und Schutzimpfung bei Tuberkulose, Deutsche med. Wchnschr. **49**:1197, 1923.

61. Haupt, H.: Die Bekämpfung der Rindertuberkulose mit Hilfe abgeschwächter Tuberkelbazillen, Ztschr. f. Tuberk. **33**:157, 1920.

62. Shiga: Studien über das Tuberkulosevaccin. Sero-vaccin aus den avirulenten, lebenden Tuberkelbazillen, Kitasato Arch. Exper. Med. **1**:157, 1917.

power of stimulating resistance. Vaudremer and Mondet⁶³ claim that they have immunized guinea-pigs successfully by inoculation with a strain of bacilli rendered non-acid-fast as well as avirulent by growth on potato broth without glycerol. Such attempts have been numerous both before and after Calmette's elaborate and long continued experiments with tubercle bacilli reduced to avirulency by prolonged cultivation on mediums containing bile. There is no theoretic reason why bacilli attenuated by such means should not be as effective in stimulating resistance as the "biliated bacilli." No other such method, however, has been on continuous trial for as long as the Calmette method, and for that reason as well as their empiric impressiveness, the experiments of Calmette have been considered in detail, and others of similar nature only mentioned.

MECHANISM OF INFECTION—IMMUNIZATION

The experiments cited so far were concerned chiefly with the development of an increased resistance which prevented animals from acquiring tuberculosis. In many of them little attention was paid to the manner in which infection was warded off, or the changes occurring in different organs on reinfection. Trudeau, Römer, Calmette and Selter, however, have all recognized the relation of hypersensitiveness and the Koch phenomenon to increased resistance to tuberculosis.

Numerous investigations have dealt with tissue resistance rather than general resistance. Römer was as much impressed by this as by the phenomenon of general increased resistance, and published photographs of skin lesions at the site of inoculation on first infection and superinfection. More investigations have dealt with increased skin resistance than with heightened tissue resistance elsewhere, presumably because the Koch phenomenon was first described for the skin, and because skin lesions are readily observed and followed during life.

Not a few observers have seen in the Koch phenomenon not merely a manifestation of immunity but the cause itself. Koch⁶⁰ apparently believed that in the sloughing which followed the necrosis at the site of reinfection the reinfecting bacilli were wholly cast out from the body, and hence unable to set up a general invasion. Della Cella,⁶⁴ who produced the Koch phenomenon several times in the same animal with rapid sloughing and healing each time, emphasized the sloughing, but considered bacteriolysis possible. Bezançon and Serbonnes,⁶⁵ who describe

63. Vaudremer, A., and Mondet, G.: *Essai de vaccination antituberculeuse de cobaye*, *Compt. rend. Soc. de biol.* **92**:558, 1925.

64. Della Cella, F. A.: *Ueber das Verhalten tuberkulöser Tiere gegen die subkutane Infektion mit Tuberkelbazillen*, *Zentralbl. f. Bakteriologie, I. Orig.* **36**:12, 1904.

65. Bezançon, F., and de Serbonnes, H.: *Superinfection tuberculeuse expérimentale du cobaye. Etude des phénomènes allergiques cutané et pulmonaire*, *Ann. de méd.* **1**:129, 1924.

several variations of the phenomenon, also adhered to the idea of evacuation in dead tissue, stating that following inoculation in the already infected animal tubercle bacilli were to be found microscopically only in the necrotic zone at the site of injection.

In a long series of papers appearing chiefly in the *American Review of Tuberculosis*, Krause has repeatedly called attention to the factors underlying the Koch phenomenon. These are clearly outlined in a brief summary by Krause⁶⁶ and in a later paper with experimental details by Krause and Peters,⁶⁷ in which a series of plates are published illustrating the course of cutaneous infection in the normal and already tuberculous animal. The accelerated development of tubercle, regardless of whether or not sloughing occurs, is emphasized as an essential feature in the mechanism of immunity. Necrosis and sloughing occur with the larger doses; immunity to reinfection, however, is manifested just as clearly to smaller infections in which sloughing does not occur and the reinfecting bacilli remain in the tissue. The authors summarize the points of contrast on infection in normal and tuberculous guinea-pigs as follows: (1) an immediate reaction on the part of the tuberculous animals which is absent in the normal; (2) an early development of nodule in the former which is again lacking or less well defined in the controls even at the end of a week; (3) a tendency of the lesions in the tuberculous soon to come to a standstill, while at the same time (two weeks) those in the control are now rapidly advancing; (4) a later tendency of the lesions in the tuberculous animals to retrogress and heal, while those in the controls persist and progress. In brief, the important basic facts are a sluggish tissue reaction to primary infection and a rapid one to reinfection.

Krause and Peters call attention to the fact that the reaction in the tuberculous animal is not merely inflammatory or inflammatory and destructive. The exudative phenomena of allergy, to which early observers of allergy had paid particular attention, is accompanied and succeeded by early proliferation of the fixed tissue cells. The extraordinary fact is that allergy is not merely an altered tissue capacity for reaction, but a phenomenon extending to each of the cells taking part in the formation of this tissue, including the fixed tissue "epithelioid" cells. As Krause puts it, "infection 'trains' or 'sensitizes' these cells (in our present ignorance of underlying factors it is hard to find more accurate words),

66. Krause, A. K.: Cellular or Tissue Immunity to Tuberculosis and Its Relation to the Pathology of Tuberculosis, Tr. Nat. Assn. Study Prev. Tuberc., 1916, p. 253.

67. Krause, A. K., and Peters, D.: A Description of Graphic Records of the Local Allergic and Immune Reactions to Tuberculous Reinfection in Guinea Pigs, *Am. Rev. Tuberc.* 4:551, 1920.

so that their irritability now becomes greatly enhanced. When, therefore, reinfections occur these cells react even to very small ones with the speed and vigor that once characterized their response to very large first infections." An outstanding mechanism in the immunity displayed by the tuberculous animal is therefore the rapid formation of anatomic tubercle which tends to limit the spread of the infection.

This conception is later elaborated by Krause in a series of papers with Willis. Krause⁶⁸ had previously shown that when normal guinea-pigs received a first infection subcutaneously rapid lymphatic distribution began with early generalization of infection. It appeared that within the first four days after infection bacilli had made the complete circuit of the body, for inoculation of spleen, lung and tracheobronchial lymph node tissue into new guinea-pigs, disclosed within four days the presence of tubercle bacilli in these organs. When, however, the same method was applied by Krause and Willis⁶⁹ in the study of guinea-pigs already tuberculous, but with a mild localized infection with an organism of low virulence, a much different rate of dissemination was observed. In the immunized animals there was a great delay in the appearance of virulent bacilli at points distal to the portal of entry. During the first two weeks none reached the internal organs. Nevertheless, the virulent bacilli had not been destroyed at the site of inoculation, for after a month virulent bacilli could always be found in the lungs, spleen and tracheobronchial lymph nodes. "The immune state of the guinea pig to tuberculosis is thus seen to consist not so much in a complete destruction or fixation of bacilli at the portal of entry, but in a considerable retardation of their speed through the body." More remarkable still, however, was the fact that although tubercle bacilli in the immunized animals did reach the internal organs by the end of the first month, it was two or three months before tubercles were visible, and ten or eleven months before generalization of tuberculosis took place.

The histologic picture during the long interval between first detection of tubercle bacilli and the development of macroscopic tubercle is not given. It is hard to believe that microscopic tubercles were not present. One at once thinks of the apparent extraordinary tolerance of the human tracheobronchial lymph nodes to the presence of tubercle bacilli when there is extensive ulcerative and bronchopneumonia tuberculosis of the lungs. The lymph nodes are almost never caseous, and only those

68. Krause, A. K.: Tuberculosis in the Guinea Pig after Subcutaneous Infection, with Particular Reference to the Tracheo-Bronchial Lymph Nodes, *Am. Rev. Tuberc.* 4:135, 1920.

69. Krause, A. K., and Willis, H. S.: Dissemination of Virulent Tubercle Bacilli after Infection and Reinfection, *Tr. Nat. Tuberc. Assn.*, 1924, p. 277. The Rate of Dissemination of Virulent Tubercle Bacilli in Normal and Immune Guinea Pigs, *Bull. Internat. Union against Tuberc.* 1, No. 3, 1924.

nearest the lung are greatly enlarged. Tubercles cannot be seen with the naked eye. Yet microscopic examination always discloses scores of epithelioid tubercles, and the impression is unavoidable that tubercle bacilli are reaching these nodes in a constant stream, and are held in check by a prompt reaction of the same type which Krause describes as such an important limiting factor on subcutaneous reinfection in animals. Willis,⁷⁰ in elaborating these experiments, has suggested this probability.

By excision of tissue at the site of intracutaneous inoculation Krause and Willis were able to determine the time at which dissemination took place. If excision was delayed until twenty-four hours in nonimmune animals, tubercle bacilli invariably had spread from the site of inoculation, and generalization of the infection occurred. In the immunized animals, on the other hand, if excisions were made within the first four days after inoculation no tuberculosis would occur. This is in marked contrast to the fact that dissemination occasionally occurred in the first hour and always during the first twenty-four hours in nonimmunized animals.

Willis⁷¹ has elaborated and discussed these experiments in two later papers, in which the details of the methods used by Krause and Willis are published. Further confirmation is afforded of the hypothesis of Krause that specific immunity to reinfection is accomplished in part through a fixation of bacilli of reinfection by the rapid inflammatory response of the allergic reaction. Several questions still not altogether solved are again raised, chief of which are: Does a bacteriolysis occur at the site of reinfection, with the result that fewer bacilli reach the animal tissues? Is some change produced in the virulence of the bacilli after their inoculation into sensitive tissues? Does the local allergic reaction at the point of second and later focalization aid in the protection? The first and third are left open. The second is considered improbable, because bacilli recovered after generalization of infection in animals previously infected have preserved their full virulence for new animals.

Among others who have studied the phenomenon of cutaneous reinfection are Rist and Rolland.⁷² These investigators could not accept the hypothesis advanced by Bezançon and Serbonnes that immunity to

70. Willis, H. S.: The Early Dissemination of Tubercle Bacilli After Intracutaneous Inoculation of Immune Guinea Pigs of Reinfection, *Am. Rev. Tuberc.* **11**:439, 1925.

71. Willis, H. S.: The Early Dissemination of Tubercle Bacilli After Intracutaneous Inoculation of Guinea Pigs of First Infection, *Am. Rev. Tuberc.* **11**:427, 1925; also Footnote 70.

72. Rist, E., and Rolland, J.: Etudes sur la réinfection tuberculeuse et le phénomène de Koch, *Ann. de méd.* **2**:13, 1914.

reinfection resulted from evacuation of the reinfecting bacilli in the slough from the acute, necrotizing lesion produced. Rist and Rolland noted rapid disappearance of many of the reinfecting bacilli and modification in the form and staining of the remainder, as well as decrease in their infecting power for the normal guinea-pig. In the absence of the quantitative factor claims as to the virulence of the bacilli left at the site of reinoculation are not of much value, but previous studies on the peritoneum as well as the work of others had given them much evidence for bacteriolysis in the reinfected animal, and they believed the same factor operated in the skin.

The experiments on the peritoneum were conducted by Rist, Leon-Kindberg and Rolland⁷³ and were based to some extent on previous observations of Bail.⁷⁴ Bail had found that guinea-pigs withstood enormous doses of tubercle bacilli without immediate intoxication, but later died with generalized, including peritoneal, tuberculosis; but previously infected pigs died in a few hours with intense peritoneal exudation and profound intoxication on intraperitoneal injection of a small dose of bacilli. In the exudate mononuclear cells predominated, and phagocytosis by the large mononuclears was active. Tuberculin alone produced death in the same manner. These experiments formed the basis for Bail's famous theory of "aggressins."

Rist, Leon-Kindberg and Rolland to a large extent confirmed these observations, but added that polymorphonuclears were prominent in the exudate of reinfection. They noted also that while bacilli preserved their form and acid-fastness in normal animals, those in the allergic animal became granular and tended to disappear. The most remarkable result, however, was the fact that if an animal survived reinfection with a small dose it lived to develop generalized tuberculosis without peritoneal involvement, whereas in the animals never previously infected, tuberculous granulation tissue locally, as well as ultimate generalized tuberculosis, developed on intraperitoneal infection.

Rist and Leon-Kindberg⁷⁵ had previously demonstrated an allergic response in the kidney on intracardiac injection of bacilli into an already infected animal. Hemorrhage and diffuse necrosis occurred. The authors believed that certain types of acute kidney pathology seen in spontaneous disease in man have a similar allergic basis. Rist and his

73. Rist, E.; Leon-Kindberg, M., and Rolland, J.: Etudes sur la réinfection tuberculeuse, *Ann. de méd.* 1:310, 1914; Etudes sur la réinfection tuberculeuse. II. La bacteriolyse intraperitoneale chez le cobaye tuberculeux, *ibid.*, p. 375.

74. Bail, O.: Ueber Empfindlichkeit bei tuberkulösen Tieren, *Wien. klin. Wchnschr.* 17:846, 1904; Der akute Tod von Meerschweinchen an Tuberkulose, *ibid.* 18:211, 1905.

75. Rist, E., and Leon-Kindberg, M.: Lesions rénales obtenues par l'injection intra-cardiac de bacilles tuberculeux chez des chiens atteint de tuberculose chronique, *Bull. soc. et sc. sur la tuberc.*, ser. 2 3:29, 1913.

collaborators also cited the common tuberculid as an example of endogenous reinfection of the skin in which the infecting organisms had been destroyed by the defensive forces. Their work emphasized the peculiar paradox that virulent "tubercle bacilli were uniquely fatal but nontoxic for animals not previously infected, and uniquely toxic but not fatal (in small enough dosage) for the infected." The violent reaction which halts the invader may kill the host, a manifestation of immunity which Krause has aptly termed "the two edged sword of allergy."

Attempts to reproduce the Pfeiffer phenomenon with tubercle bacilli were several times made before the experiments of Rist, Leon-Kindberg and Rolland. Deycke and Much⁷⁶ found that lysis occurred on injection of tubercle bacilli into the guinea-pig, especially in one already infected, and Much and Leschke⁷⁷ found phagocytic action intense in animals immunized with the acid treated, dead bacilli concerning the immunizing properties of which Much has written so frequently. They were not able to prove for a certainty that lysis had occurred, but tubercle bacilli were taken up rapidly by phagocytes and most disappeared altogether, a finding indicating to the authors that lysis must have occurred.

Kraus and Hofer⁷⁸ carried out a more extensive investigation in which fluid was drawn from the peritoneal cavity of intraperitoneally reinfected guinea-pigs at intervals after the second infection. In such animals mononuclear exudation occurred, red staining bacilli (Ziehl-Neelsen stain) rapidly became few in number, and granular blue bacilli became numerous. In normal animals the injected bacilli remained extracellular for the most part and preserved the normal staining capacity.

A typical experiment reads as follows: Guinea-pigs were infected with bovine type tubercle bacilli. Three months later bacilli of the same type were injected intraperitoneally. Within fifteen minutes, an intense mononuclear exudation occurred. Tubercle bacilli were still extracellular but becoming granular. At the end of the forty-five minutes, granules were more numerous than bacilli; phagocytosis of most of the bacilli had occurred. At the end of three hours, none remained extracellular. They claimed a high degree of specificity for this intraperitoneal lysis, serving for differentiation within the acid-fast group.

76. Deycke, G., and Much, H.: *Bakteriolyse von Tuberkelbazillen*, München. med. Wchnschr. **56**:1985, 1909.

77. Much, H., and Leschke, E.: *Das biologische und immunisatorische Verhalten der Tuberkelbazillenauflösung nebst Tuberkulinstudien und Tuberkuloseimmunitätsstudien*, Beitr. z. klin. Tuberk. **20**:405, 1911.

78. Kraus, R., and Hofer, G.: *Ueber Auflösung der Tuberkelbazillen und anderer säurefester Bakterien*, Wien. klin. Wchnschr. **25**:1111, 1912; *Ueber Auflösung der Tuberkelbazillen im tuberkulösen Organismus*, Zentralbl. f. Bakteriologie. I. Ref. **54**:191, 1912.

Substances favoring lysis, according to Kraus and Hofer, could be detected also in the serum of tuberculous patients and guinea-pigs, and to a less extent in normal serum. Their conclusion was that the tuberculous organism produced lysins for tubercle bacilli in high degree, and that these had much to do with spontaneous healing and immunity in tuberculosis.

The experiments of Manwaring and Bronfenbrenner⁷⁹ supported this work. They found that tubercle bacilli injected into the peritoneal cavity of tuberculous guinea-pigs, rats, rabbits, dogs and monkeys rapidly disappeared from the peritoneal fluid but persisted in normal controls. This lysis was considered to be largely the result of tissue fixation. Serum alone did not cause it, and lysis was assumed to take place in the fixed peritoneal cells. Moreover, the property could not be transferred through the serum of infected animals to the cells of the noninfected. In this experiment the process of lysis was not actually observed, but was assumed to occur, because of the rapid disappearance of bacilli. The phenomenon could be demonstrated *in vitro*. Bacilli brought into contact in tubes with the serosa of isolated intestine from tuberculous guinea-pigs rapidly vanished, while this phenomenon did not occur when the intestine of a normal animal was substituted.

Wolff-Eisner,⁸⁰ noted for his lytic theory of the action of tuberculin, upheld the theory of antibodies and bacteriolysis in tuberculosis, and considered humoral immunity of even more importance than cellular.

Römer⁸¹ was unconvinced. In the serum of his immune animals he often found specific antibodies. They were, however, occasionally absent in highly immunized animals. Therefore no antibody content could explain immunity, and Römer saw no evidence that the mechanism of tuberculosis immunity consists in a destruction of the entering bacilli. Krause⁸² is not satisfied with the evidence respecting bacteriolysis.

Burnet,⁸³ on repeating the work of Kraus and Hofer and Manwaring and Bronfenbrenner, was certain that the bacilli which disappeared from the peritoneum were not destroyed, but were taken up by fixed tissue phagocytes. Much tuberculosis of the omentum developed later from their presence. No Pfeiffer phenomenon occurred, but many of the bacilli, on the other hand, were probably destroyed slowly in the phagocytic cells.

79. Manwaring, W. H., and Bronfenbrenner, J.: Intraperitoneal Lysis of Tubercle Bacilli, *J. Exper. Med.* **18**:601, 1913.

80. Wolff-Eisner, A.: Die histiogene und die humorale Tuberkuloseimmunität, *Arch. f. Dermat. u. Syph.* **132**:553, 1921.

81. Römer, P., and Joseph, K.: Beitrag zum Wesen der Tuberkulose-Immunität-Antikörperstudien, *Beitr. z. klin. Tuberk.* **17**:365, 1910. Also footnote 3.

82. Krause, A. K.: *Environment and Resistance in Tuberculosis*, Baltimore, Williams & Wilkins Company, 1923, p. 96.

83. Burnet, E.: La pretendue destruction des bacilles de Koch dans le peritoine des cobayes tuberculeux, *Ann. de l'Inst. Pasteur* **29**:119, 1915.

Baatz⁸⁴ was instigated by Pfeiffer, who gave the first clear demonstration of specific bacteriolysis, to study lysis of the tubercle bacillus. He was unable to confirm Much, Kraus and Hofer and others who claimed that lysis of tubercle bacilli occurred on injection into an immunized animal. No specific lysis could be observed in the omentum in tuberculous guinea-pigs killed from thirty minutes to twenty-four hours after intraperitoneal reinfection.

The most recent experiment on the peritoneum is that of Gardner and his associates,⁸⁵ who found that primary infection led to an exudate which subsided in twenty-four hours, while superinfection led to a more copious exudate which persisted. It was demonstrated by vital staining that the two differed in that a monocystosis occurred in primary progressive tuberculosis, while lymphocytosis predominated in the fluid of the superinfected animal. In common with Cunningham and Sabin, Gardner believes that the epithelioid cell of the tubercle is derived from the monocyte. The report published is preliminary and work is in progress.

The reaction of serous membranes to reinfection has also been studied by Paterson and Soper and Dworski. Paterson⁸⁶ found that intrapleural inoculation of tubercle bacilli into normal guinea-pigs elicited no noticeable pleural reaction, while in pigs with a mild localized tuberculosis there occurred an exudation of serum, leukocytes, red blood cells and fibrin. However, the acute pleural reaction in tuberculous animals tended to localize the infection, and such animals outlived controls inoculated primarily with the same dose of bacilli in the pleural cavity. Paterson, following the lead of Krause, attributed pleural effusions occurring in man to allergic response to endogenous reinfection.

Soper and Dworski⁸⁷ found the phenomena of allergy and superinfection manifest in the meninges of the rabbit as in other organs and serous membranes. With relatively high doses of reinfecting bacilli, death was hastened by allergy. After small doses the superinfected animals appeared to throw off the disease temporarily and survived much longer than controls receiving a primary infection of the same size intrameningeally. Spinal fluid examinations showed an intense, immediate meningeal reaction in the superinfected rabbit. In the control animals

84. Baatz: Zur Frage der Auflösung von Tuberkelbazillen durch spezifische Immunstoffe, *Zentralbl. f. Bakteriol. I. Orig.* **84**:81, 1920.

85. Dworski, M.; Smith, D. I., and Gardner, L. U.: A Comparative Study of the Cytological Reactions to Primary and Superinfection with the Tubercle Bacillus in the Guinea Pig, *Tr. Nat. Tuberc. Assn.*, 1925, p. 321.

86. Paterson, R. C.: The Pleural Reaction to Inoculation with Tubercle Bacilli in Vaccinated and Normal Guinea Pigs, *Am. Rev. Tuberc.* **1**:353, 1917.

87. Soper, W. B., and Dworski, M.: Experimental Tuberculous Meningitis. Superinfection of the Meninges in Rabbits, *Am. Rev. Tuberc.* **11**:200, 1925.

a slow, irregular, gradual increase in cells of the spinal fluid followed primary meningeal infection. The authors were uncertain as to whether bacteriolysis occurred in the superinfected animals or not.

Soper⁸⁸ previously, at the suggestion of Krause, had studied reinfection in the rabbit liver in somewhat the same manner that Nichols⁷ had studied experimental reinfection in the rabbit lung. Rabbits first infected with human type tubercle bacilli, which does not set up generalized tuberculosis in the rabbit, when small doses are used, proved highly resistant, as compared with nonvaccinated controls, to reinfection through the portal vein with virulent bovine type bacilli. An early and intense involvement of the liver occurred on superinfection, which, however, tended to abort the infection, the superinfected animals long outliving the controls, in which the liver infection developed more gradually. It was noteworthy, however, that the reaction in the superinfected animal differed only quantitatively from that in the control. The type of cell concerned in the reaction was the same in the two cases.

Long⁸⁹ carried out a similar study on the guinea-pig testis. The results were summarized as follows:

(1) Guinea-pigs already infected with tuberculosis respond to tubercle-bacillus infection of the testicle within twenty-four hours with marked hyperemia and swelling of the organ, interstitial edema, intracellular edema and beginning necrosis of the spermatocytes and spermatids, and an intense wandering cell infiltration in which epithelioid and round cells are conspicuous. Infection of the testicle of the nontuberculous guinea-pig leads, within twenty-four hours, to very slight changes.

(2) In the previously infected animal coagulation necrosis of the tubular germinal epithelium follows the primary swelling, and absorption of necrotic tissue and steady increase in epithelioid cells go on together. In the animal previously not infected epithelioid cell infiltration soon becomes intense, with extensive absorption of testicle tubules, which, however, do not go through the stage of coagulation necrosis noted in the already tuberculous animal. After three to four weeks the lesions may look alike, except that there is a tendency to more marked epithelioid cell proliferation and to the growth of fibroblasts on the part of the testicle of the sensitized animal, while in the testicle of the nonsensitized animal there is a less marked epithelioid reaction and a definite tendency to caseation necrosis.

(3) Unless the results are modified by suppuration, which may intervene in either group, the testicle of the immunized animal is apt, after six weeks, to be densely infiltrated with epithelioid cells and moderately fibrous, with little necrosis, while that of its nonimmunized mate may be largely necrotic, with a much less extensive epithelioid cell and fibroblast reaction. Corresponding to the greater density of epithelioid cells there is a coarser deposition of reticulin in the

88. Soper, W. B.: Experimental Tuberculosis of the Liver, *Am. Rev. Tuberc.* 1:385, 1917.

89. Long, E. R.: Tuberculous Reinfection and the Tuberculin Reaction in the Testicle of the Tuberculous Guinea Pig, *Am. Rev. Tuberc.* 9:215, 1924.

testicle of the immunized animal. In neither case is there the slightest spermatogenesis, nor do many tubules remain recognizable.

(4) Generalization is earlier and more extensive in the nonimmunized animal. Infection of the opposite testicle, hematogenous or by extension, is likely to occur late in the nonimmunized guinea pig. It has not been observed in the immunized.

In this study, with the doses used, abortion of the infection was never observed. Necrosis always followed the superinfection. On the other hand, scar tissue proliferation was much more intense in the superinfected than in the control animals, and corresponding to this, and probably preparing the way for it, was an earlier and more rapid deposition of reticulum than in the nonimmunized animals. Long and Miller,⁹⁰ comparing the rate of reticulum deposit in experimental tuberculosis in primary infection and superinfection, have correlated the amount present directly with the extent of infiltration of the large mononuclear wandering cells, and have raised the question whether this plays a rôle in the defensive mechanisms of the immunized animal. It appears to be a precursor to the important encapsulating fibrous tissue, and it is also a possibility that from the start it aids in that limitation of spread of infection in reinfected animals shown so clearly in the experiments of Krause and Willis.

One of the most elaborate histologic investigations on superinfection is that of Baldwin and Gardner.⁴ These authors give a review with extensive bibliography of the whole matter of reinfection, including experiments on superinfection and clinical observations on both exogenous and endogenous reinfection, recording at the same time observations of their own on inhalation reinfection in guinea-pigs with mild, localized tuberculosis. The reaction to reinfection in these pigs consisted in accumulation of cell plaques and isolated mononuclears within the alveoli, as in the initial reaction to a primary infection, but with exudation of polymorphonuclears, eosinophils and fibrin in addition. The nodule thus formed did not have the regular outlines and compact structure of a tubercle resulting from primary inoculation. Caseation occurred only rarely, the tendency being for the exudate and proliferated cells to disappear, leaving only a moderate thickening of the alveolar walls in a circumscribed focus, which persisted indefinitely. "It is evident that the allergic reactions initiated in the guinea pig's lung by the inhalation of small doses of the R₁ strain are manifested by a very moderate localized inflammation accompanied by atypical and abortive tubercle formation. The reaction remains localized, does not tend to spread within the lung and practically never caseates." Baldwin and Gardner were unable to detect tubercle bacilli in stains of the allergic

90. Long, E. R., and Miller, W. S.: Reinfection and Reticulum Formation in Experimental Tuberculosis, *Tr. Nat. Tuberc. Assn.*, 1924, p. 285.

lesion, and suggest that bacteriolysis had occurred. However, as reinoculation of such tissue established the viability of bacilli present, they feel that possibly change in the tinctorial properties of the bacilli accounted for failure to find them.

A recent study of the histologic features of the lesion of superinfection has been added by Jaffé and Löwenstein,⁹¹ who confirm others that the outstanding features of the lesion of reinfection are leukocytic exudation and necrosis, with phagocytosis of the tubercle bacilli.

CONCLUSIONS

From the great body of evidence cited in the preceding pages, it may be concluded beyond question that heightened resistance to reinfection, which may reach a high degree, is conferred by primary mild infection. Whether this is "immunity" or not is aside from the point. If the condition existing after vaccination with cowpox virus or after recovery from typhoid fever is taken as typical of the truly immune state, there is much reason to feel with Pfeiffer,⁹² that "there is no real immunity to tuberculosis; all that occurs is a greatly enhanced resistance." But this greatly enhanced resistance is nothing less than immunity to infecting doses below a certain size. And from Römer to the present day hardly an investigator of note has recognized the fact of this immunity without in some way or other correlating it with the other great fact of allergy. There is not so general agreement that only infection is able to establish both states. Since the time of Trudeau it has been known that the hypersensitive state follows injection of dead tubercle bacilli, but most investigators have found this transitory and of relatively low degree. And like Trudeau, most investigators have found that "the introduction of living bacilli appears necessary for the production of relative immunity," and only that point of view has been considered in the present article.

This view has never been more concisely stated than by Krause,⁹³ who says:

Ever since the discovery of the tubercle bacillus there have been increasing efforts to attain active immunization against infection through the use of almost numberless derivatives and variants of tubercle bacilli. But competent and unbiased observers are agreed that only one procedure is uniformly successful. This consists in preliminary infection with living tubercle bacilli. . . . Out of a wealth of experiment and investigation of the immune state in tuberculosis have come several features which appear with such uniformity and consistency that

91. Jaffé, R. H., and Löwenstein, E.: *Das histologische Reaktionsbild der tuberkulösen Reinfektion*, Beitr. z. klin. Tuberk. **50**:129, 1922.

92. Pfeiffer, R.: Discussion at Freien Vereinigung für Mikrobiologie, Jena, 1920, Zentralbl. f. Bakteriologie, Beiheft. **85**:41, 1921.

93. Krause, A. K.: *Environment and Resistance in Tuberculosis*, p. 91 ff.

we are justified in formulating them as laws of specific immunity to tuberculous infection. They may be summarized as follows: (1) Specific immunity exists only in animals which at the same time have tubercle provoked by tubercle bacilli; (2) it first appears about the time of the first palpable development of the foci of infection; (3) it persists, in some degree, as long as infection remains; (4) it diminishes with the subsidence and healing of infection; (5) it increases with the extension and evolution of infection; (6) it probably disappears with the enucleation of all foci; (7) it varies in degree directly with the virulence of the immunizing microorganism; or, otherwise expressed, with the amount and activity of infection in the host. It is of the utmost significance that the conditions of allergy exactly parallel those of specific immunity; and this circumstance is true of allergy alone, among all the specific changes of reaction (including experimental production of antibodies) which may be artificially brought about in animals through the bacillus or substances derived from it. . . . This close and direct parallelism of allergy and specific immunity at once suggests that immunity is a function of allergy.

But if allergy is the underlying force which enables a tuberculous animal to abort an infection which produces progressive disease in a noninfected and therefore nonallergic control, we are as yet unable to state with precision the manner in which it does so. We may dismiss the old idea that a sloughing away of the infected region evacuates the reinfecting bacilli. The same immunity shown by Koch for the skin in 1891, has since been proved to hold for the lung, the liver, the peritoneum, pleura, meninges and testis, in which ulceration and sloughing cannot occur as in the skin. In some way or other the spread of infection is checked by the exudation and subsequent proliferation at the site of reinfection. Some authors look on the allergic response as nothing more than a rapid mobilization of the same forces which operate slowly in the normal animal. But this is not the whole story. Krause, who has emphasized this allergic effect more strongly than any other man in this country, and has elaborated a mechanical theory to account partly for the arrest of infection at the point of inoculation, himself is far from inclined to attribute immunity against reinfection to the allergic state solely. Lymphatic blocking and still unknown factors enter in, and Krause⁹⁴ states that he has seen high immunization persist when sensitization is at an extremely low ebb. The fact noted by Hamburger,⁹⁵ Calmette,⁴² Krause and Willis,⁶⁰ and others, that virulent bacilli may persist for a long time in certain tissues of the immunized body without setting up visible lesion, is important, but still unexplained.

Any hypothesis for the mechanism of immunization must agree with the facts of clinical observation and postmortem evidence in man. As Kauser⁸⁵ points out, there is abundant evidence that men pass through

94. Krause, A. K.: Personal communication.

95. Hamburger, F.: Ueber tuberculöse Exazerbation, *Wien. klin. Wchnschr.* 24:859, 1911.

a period of high degree sensitiveness to tuberculin, which wanes as the interval since the first infection increases, and yet remain resistant to reinfection as far as can be told from comparison with their fellow men who are exposed to exogenous infection to the same degree. Krause has raised the question of the localizing effect of lymphatic blockage to account for this undeniable resistance. Baldwin⁴ is doubtful as to whether tissue cells ever lose their ability to react more vigorously to the presence of tubercle bacilli after having once formed tubercles, and speaks of a "latency of sensitiveness."

One of the most puzzling features in the whole field of investigation of tuberculosis immunity is the discrepancy of results with respect to bacteriolysis. Part of the difficulty is more apparent than real, for several investigators who insist that extracellular lysis does not occur, are willing to admit that lysis may occur in phagocytic cells. After all, as Wells⁹⁶ has repeatedly pointed out, the process of lysis is essentially of the same character in the two instances. And there is almost complete agreement that phagocytosis is more active in the immunized and allergic animal than in the animal infected for the first time.

The conception of tubercle bacillus destruction is almost essential to any theory of tuberculosis immunity. There is only one to replace it, the excretion theory of Calmette. In considering this problem, I always revert to the most striking manifestation of tissue immunity with which I am familiar, the high degree of resistance of the human adult tracheo-bronchial lymph nodes to infection in the presence of massive consumption of the lung. Partial lymphatic blockage and constriction, which undeniably exist in these adults, cannot entirely account for this resistance, for bacilli get through in a constant stream, as shown by the invariable presence of epithelioid tubercles in several stages in these nodes. What becomes of the tubercle bacilli which set up these microscopic lesions? If locally excreted it could only be into the lymph stream, which would eventually bring them back to the lung. Most pathologists are content to assume that they are destroyed, but no one of them has come forward with visible and acceptable proof of the destruction. The problem of tubercle bacillus lysis or disintegration in the body should still be one of the most fruitful lines of investigation in the study of tuberculosis, even though the demonstration of bacteriolysis in the immunized tissues would not explain the whole mechanism of resistance in the immunized animal.

96. Wells, H. G.: *The Chemical Aspects of Immunity*, New York, Chemical Catalog Co., 1925, p. 236.

Notes and News

Death of Dr. Puppe.—Dr. George Puppe, professor of legal medicine in the University of Breslau, one of the editors of *Deutsche Zeitschrift für die gesamte gerichtliche Medizin*, and a leading worker in his field, died on Nov. 20, 1925.

Dr. Amaral to Organize Laboratory.—The *Brazil Medico* states that Dr. Afranio Amaral, formerly head of the Butantan Institute, has been requested by Harvard University to organize the laboratory for research on animal venoms there.

Alvarez Goes to Mayo Foundation.—Dr. Walter C. Alvarez, associate professor of research medicine in the Hooper Foundation, University of California, has accepted an associate professorship of medicine in the Mayo Foundation in Rochester, Minn. Dr. Alvarez will devote himself to research in digestion.

Lambert Goes to Porto Rico.—Dr. Robert A. Lambert has returned from São Paulo, Brazil, where since 1921 he has been director of the pathologic institute, and has assumed charge of the school of tropical medicine established by Columbia University at Porto Rico in cooperation with the University of Porto Rico.

Nicolle in Buenos Aires.—Professor Charles Nicolle, director of the Pasteur Institute of Tunis, has accepted the invitation of the Argentine government to give a course in the bacteriologic institute at Buenos Aires with conferences on typhus fever, recurrent fever and allied topics, and to inspect the sanitary conditions in some of the provinces.

Dr. Chagas Presented with Medal.—Dr. C. Chagas, chief of the public health service of Brazil, was presented with the honorary gold medal of the Hamburg medical faculty when he spoke recently at the Institute for Tropical Diseases on "Chagas' Disease: Brazilian Trypanosomiasis." He delivered a similar address before the Medical Society of Berlin.

Memorial to Ransom.—A committee consisting of M. C. Hall and E. B. Cram (secretary) of the Department of Agriculture; C. W. Stiles, of the Public Health Service; H. J. Nichols, of the Army Medical Corps, and W. W. Cort, of the Johns Hopkins University, has been considering a proposal to establish a memorial to Dr. Brayton H. Ransom, who at his death was chief of the zoological division of the Bureau of Animal Industry, and who ranked as one of the foremost parasitologists.

New Laboratory for the Medical Research Council of England.—The Medical Research Council of England is having a new laboratory built at Millhill, Middlesex, for the use of Dr. W. E. Gye and J. E. Barnard in their studies of cancer. It is expected that the building will be finished by next March, at which time the two investigators, who at present often are working five miles apart, will be able to continue their experiments together under greatly improved conditions and with a larger staff of assistants.

Dr. Crowell Becomes Associate Director of American College of Surgeons.

—Dr. Bowman C. Crowell (McGill, 1904) has resigned his position as professor of pathology in Jefferson Medical College, Philadelphia; the resignation takes effect in June, 1926. Dr. Crowell has accepted the position of associate director of the American College of Surgeons in charge of the division of clinical research.

Death of Hlava.—Jaroslav Hlava, 1855-1925, professor of pathologic anatomy in the Czech University in Prague since 1883, was a great teacher, beloved by his pupils, and a successful leader in medicopolitical affairs, particularly in the reorganization of public health measures after the war. He enjoyed in high degree the respect and cooperation of his German confreres. Hlava made significant contributions to the study of exanthematic diseases, hemorrhagic pancreatitis and uremia and wrote a textbook on pathology. He was one of the editors of *Časopis lékařův českých*. The new Czech pathologic institute in Prague bears his name.

Eugen Fränkel 1852-1925.—While a nose and throat specialist, Fränkel became largely by his own efforts a leading pathologist. He was for more than thirty years pathologist at the Eppendorfer Krankenhaus in Hamburg and became the first professor of pathology in the University of Hamburg (founded in 1919). He was a stimulating teacher and a productive worker, especially in the field of bacterial pathogenesis. He was not, as is sometimes stated, the discoverer of the pneumococcus—that distinction belongs to Albert Fraenkel (1848-1916). Volume 246 (1923) of *Virchow's Archiv* is dedicated to Eugen Fränkel by his associates and pupils on his seventieth birthday.

Banting Research Foundation.—The endowment of the Banting Research Foundation will be invested under the direction of the board of governors of the University of Toronto, who will act as trustees. They will pay to the governing body of the foundation the annual income from the endowment for disbursement. The *Canadian Medical Association Journal* says that the income from \$500,000 is considered sufficient to support the foundation for some years; it is proposed to make the funds available to assist research workers either working independently or in any other university in Canada. The foundation has been established with a view to discovering means for the prevention and cure of diseases which at present are considered incurable.

Death of Camillo Golgi (1843-1926).—This great histologist and pathologist died January 21 last. In 1870, soon after coming to the university at Pavia as professor and director of the cabinet for histology and general pathology, he applied silver nitrate solution to the study of the microscopic structure of nervous tissue. Golgi's methods proved to be of the greatest value in the study of the normal structure of the nervous system. His name lives in anatomy in Golgi's cell and in the organ of Golgi in tendons. Golgi's most important contribution to pathology was his work on malaria. In 1895, five years after the discovery of the malarial parasite by Laveran, he described the details of the life history of the parasite of quartan malaria in the patient's blood; a little later, he differentiated the parasites of tertian and estivo-autumnal fevers from those of the quartan and also showed that the chill coincides with the sporulation of a brood of parasites in the blood. His collected works were published in 1903. In 1906 a Nobel prize in medicine was divided between Golgi and Cajal.

Abstracts from Current Literature

Pathologic Physiology

BASAL METABOLISM IN ORGANIC HEART DISEASE. MORRIS W. LEV and W. W. HAMBURGER, *Am. Heart J.* **1**:240, 1925.

Seventy-five per cent of the cases of organic heart disease with decompensation show an increased basal metabolic rate of an average of 39 per cent above normal. This increase is not related directly to the type of heart involvement, arrhythmia, cyanosis or edema, but seems to vary only with the degree of decompensation and the cardiac and respiratory rate. The high basal rate decreases gradually with the return of compensation, but remains high or goes higher as decompensation continues or becomes more pronounced. In a case of paroxysmal tachycardia the basal metabolic rate increased 11.1 per cent during the paroxysm. In a normal subject, artificially induced tachypnea resulted in a 17.5 per cent basal metabolic rate increase. It is probable that the increased work of the heart and the increased activity of the muscles of respiration are responsible for the increase in basal metabolic rate in organic heart disease with decompensation, although the possibility of other factors may be considered, notably a thyroid factor, from transient hyperthyroidism during decompensation, or changes in thyroid circulation from long standing congestion of the superior circulation.

AUTHORS' SUMMARY.

THE CARBOHYDRATE METABOLISM OF THE MARANTIC INFANT. THE CARBOHYDRATE METABOLISM OF INFANTS WITH DIARRHEA, INFECTIONS AND ACUTE INTESTINAL INTOXICATION. F. F. TISDALL, T. G. H. DRAKE and ALAN BROWN, *Am. J. Dis. Child.* **30**:828 and 837, 1925.

There is no evidence of any abnormality of the general carbohydrate metabolism of the marantic infant other than the lowered concentration of fasting blood sugar, apparently the result of an inadequate reserve of glycogen.

In infants with diarrhea, infection or acute intestinal intoxication there is derangement of the carbohydrate metabolism not primarily associated with a deficient production of insulin.

LIVER INJURY IN THYROTOXICOSIS AS EVIDENCED BY DECREASED FUNCTIONAL EFFICIENCY. J. B. YOUNG and L. M. WARFIELD, *Arch. Int. Med.* **37**:1, 1926.

Twenty-two, or 50 per cent, of the forty-four patients in the series showed an impairment of liver function according to the tests of liver function used. Twenty-one of the twenty-seven cases satisfactorily tested showed a decreased glucose tolerance. No relation was found to exist between the functional efficiency of the liver as tested and the glucose tolerance, basal metabolic rate or other features of the disease except loss of weight. The impairment of liver function in thyrotoxicosis seems to be associated to some degree with loss of weight.

S. A. LEVINSON.

HYPERGLYCEMIA. II. PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD FROM CASES OF DIABETES MELLITUS. L. FOSHAY, Arch. Int. Med. 37:18, 1926.

In the two types of "conductivity chlorid discrepancy" in diabetes, one type is usually permanent, the other always transient. In young, untreated diabetic patients there is evidence of some diminution of the blood alkalinity at all times. This rapidly disappears under insulin treatment. In untreated, arteriosclerotic diabetic patients there is no evidence of diminished blood alkalinity unless the patient is nearly in coma. In the case of extreme exsiccation from water deprivation given here, the blood picture is shown to be similar to that which occurs in acute diabetic coma. The chief differences are the greater retention of inorganic salts and a lesser glycemia.

S. A. LEVINSON.

THE EFFECT OF HEART MUSCLE DISEASE ON THE ELECTROCARDIOGRAM. A. W. MASTER and H. E. PARDEE, Arch. Int. Med. 37:42, 1926.

Disease of the ventricular muscle plays the dominant rôle in producing abnormalities of the electrocardiographic curve by causing an abnormal development of the electric product of the contraction. If the conduction tissue becomes involved in disease of the endocardium, this also may cause changes in the curve by causing an abnormal spreading of the contraction. Each of these factors will have a variable importance in any given case.

S. A. LEVINSON.

WATER METABOLISM. E. ANDREWS, Arch. Int. Med. 37:82, 1926.

In dogs an amount of water varying from 0 to 72 cc. per kilogram of body weight is held in a loose combination with the colloids, perhaps merely acting as a solvent for the colloids and electrolytes. This water reserve in the dog is 0 at the level of 45 of the alkali reserve and rises about 10 cc. for each cubic centimeter of the carbon dioxide combining power of plasma. Certain hitherto inexplicable clinical phenomena may be explained on the basis that this water reserve is an active factor in water absorption and excretion.

S. A. LEVINSON.

GLUCOSE UTILIZATION IN RENAL GLYCOSURIA. J. E. PAULLIN, Arch. Int. Med. 37:88, 1926.

Patients with renal glycosuria metabolize and store carbohydrate in the same way as normal persons. The previous supposition, namely, that patients with renal glycosuria metabolize carbohydrate in a normal way is justified, and so far as the evidence points, they do not develop diabetes mellitus.

S. A. LEVINSON.

STUDIES ON X-RAY EFFECTS. XIV. THE EFFECT OF X-RAY ON THE DIVISION RATE OF PARAMECIUM. ROBERT T. HANCE and HARRY CLARK, J. Exper. Med. 43:61, 1925.

Two races of paramecium were submitted for varying lengths of time to irradiation, and a large number of individuals were observed to determine the effect on the rate of division. The division rate of both races suffered a slight initial depression lasting for from two to five days following the exposure. This depression was followed by complete recovery.

Within rather wide limits the length of the exposure has, in these experiments, made no appreciable difference. Apparently the maximum effect of the roentgen rays is produced by relatively short exposures. Continued radiation produces little further change until exposures of three and four hours are used, when precisely the opposite results are obtained from those obtained with shorter exposures.

Doses repeated at various intervals have in general failed to interfere more markedly with the division rate than a single dose. Repeated radiation causes the cells to become slightly swollen without apparent interference with their viability.

AUTHORS' SUMMARY.

THYMECTOMY IN THE RABBIT. CHESTER M. VAN ALLEN, J. Exper. Med. **43**:119, 1925.

The object of the present investigation was to determine whether the thymus could be completely removed from rabbits of certain ages without producing any serious disturbance of health which would interfere with their use in other experiments or complicate the interpretation of results. It was found that this could be done.

AUTHOR'S SUMMARY.

THE RELATION OF THE THYROID GLAND TO THE SURFACE TENSION OF THE BLOOD PLASMA. I. THE EFFECT OF THYROIDECTOMY. C. M. WILHELMJ and MOYER S. FLEISHER, J. Exper. Med. **43**:179, 1926.

Following thyroidectomy in guinea-pigs, there is a gradual elevation of the surface tension of the blood plasma which reaches its height in from nineteen to twenty-two days after operation. This elevation is probably permanent, since we have found it to persist for as long as one hundred and twenty days.

In our experiments, we found a few thyroidectomized animals in which the surface tension of the plasma was still within normal limits from twenty-four and one hundred and twenty days after operation. We suggest that these exceptions are due to three possible factors: (1) incomplete thyroidectomy; (2) presence of accessory thyroid tissue; (3) compensatory activity on the part of other organs.

The surface tension of the plasma from operated animals is higher than that from controls in both the initial and twenty minute determinations, but the difference is greater at the twenty minute period.

The time-drop (difference between the initial and twenty minute determinations) is somewhat greater in the plasma from normal than in that from operated animals.

It is suggested that these changes are due to a decrease in the amount of certain normally occurring surface-active substances, the production of which is directly or indirectly dependent on the thyroid gland.

AUTHORS' SUMMARY.

THE RELATION OF THE THYROID GLAND TO THE SURFACE TENSION OF THE BLOOD PLASMA. II. THE EFFECT OF THE ADMINISTRATION OF THYROID EXTRACT AND THYROXIN. C. M. WILHELMJ and MOYER S. FLEISHER, J. Exper. Med. **43**:195, 1926.

Determinations of the surface tension of blood plasma from guinea-pigs, before and after feeding thyroxin, in most cases showed a definite decrease. Of twenty-seven experimental animals, twenty showed a depression in the

surface tension which ranged from 1.9 to 13.9 dynes, with an average of 5 dynes. Six animals showed variations hardly exceeding the limits of experimental error, while one showed an elevation of 1.1 dynes.

Six normal control animals, bled on the same days and kept under identical conditions, showed differences in the two determinations which ranged from a decrease of 0.5 to an increase of 0.6 of a dyne. One other control showed a drop of 1 dyne.

Two animals which had been fed large quantities of thyroid extract over a period of ten days, gave values considerably below normal. One of these animals survived, and after eleven days, during which no thyroid extract was given, the surface tension was found again to be within normal limits.

The hypothesis is advanced that these changes are due to an increase in the amount of certain normally occurring surface-active constituents which are produced as a result of increased cellular metabolism.

AUTHORS' SUMMARY.

THE INFLUENCE OF PROTEIN INJECTIONS ON THE METABOLISM OF PERSONS WITH ALKAPTONURIA. H. BAAR and P. FREUD, *Klin. Wchnschr.* 4:2388, 1925.

An injection of serum or milk into persons with alkaptonuria is followed by an immediate drop in homogentisic acid elimination. The effect persists only two or three days.

ARTHUR LOCKE.

THE ANTAGONISM BETWEEN INSULIN AND THE HYPOPHYSIS HORMONE. J. SEREBRIJSKI and H. VOLLMER, *Klin. Wchnschr.* 4:2256, 1925.

Insulin limits the antidiuretic action of "pituglandol" although itself antidiuretic. It increases the water and salt binding power of tissue without causing essential concentration changes in the blood. The hypophysis hormone produces hydremia and increased extrarenal elimination without affecting the renal salt elimination.

ARTHUR LOCKE.

THE ACTIVATION OF INSULIN BY PROTEIN SUBSTANCES. F. BERTRAM, *Klin. Wchnschr.* 4:2285, 1925.

The action of insulin is considerably increased when injected subcutaneously or intramuscularly in admixture with protein. The largest increase is obtained by admixture of the diabetic patient's own serum. Of the single serum fractions, the globulins are most effective. The increased activity is not manifested with intravenous injection nor if the insulin and protein are administered separately.

ARTHUR LOCKE.

EXPERIMENTAL STUDY OF THE THEORY OF THE INTESTINAL FUNCTION OF LYMPHOCYTES. K. SATAKE, *Sc. Rep. Govt. Inst. Infect. Dis., Tokio* 3:121, 1924.

Using guinea-pigs especially reared to shield them from parasitic infestation, the author prepared sections from the various levels of the intestinal tract of the animals and from these estimated the lymphocytic migration. He found that the migration rate was greatest in the duodenum and the jejunum, diminishing gradually as the end of the ileum is approached. In the cecum migration is again increased, again with diminution along the course of the large intestine. These varying migration rates were evoked most strikingly by a fatty or carbohydrate diet and disappeared to a large extent with a protein diet and in

inanimation. From this, the writer infers that the lymphocytes in the intestinal tract play a rôle, the exact nature of which is still undetermined, in fat and carbohydrate digestion. In support of this view, he calls attention to the relative scarcity of intestinal lymphadenoid tissue in carnivora, and its relatively excessive development in herbivora, as well as its presence in the pharyngeal region where starch digestion begins.

H. E. EGGERS.

Pathologic Anatomy

INGUINAL ENDOMETRIOSES (OFTEN REPORTED AS ENDOMETRIAL TISSUE IN GROIN, ADENOMYOMA IN GROIN, AND ADENOMYOMA OF ROUND LIGAMENT). J. A. SAMPSON, *Am. J. Obst. & Gynec.* **10**:462, 1925.

In eight cases of "adenomyoma" of the intraperitoneal part of the round ligament, an endometriosis of other pelvic structures was present with endometrial hematoma in the ovaries of four. Sampson urges that in all the eight cases the endometriosis was due to implantation of epithelium carried through the tubes during menstruation. It seems possible that lymphatic and venous metastasis of endometrial tissue may occur in the groin and other parts.

CYSTIC LESIONS OF POSSIBLE ENDOMETRIAL ORIGIN IN APPENDIX; FOUR CASES. G. W. OUTENBRIDGE, *Am. J. Obst. & Gynec.* **10**:545, 1925.

Cysts of various sizes are described, empty or containing bloody and other débris, in the wall of the appendix or meso-appendix, but without any relation to the appendiceal mucosa, and lined with a single layer of columnar cells. All occurred in women.

MENINGITIS SYMPATHICA. ISRAEL STRAUSS, *Arch. Otolaryng.* **3**:46, 1926.

Acute suppurative conditions, either in the accessory sinuses of the cranium or in the ear and its related structures, and in the brain, frequently cause a reaction in the cerebrospinal fluid. This reaction is characterized by: (1) an increase in the amount of the fluid; (2) an increase in the albumin content, which may be moderate or considerable; (3) pleocytosis, in which generally there is an increase of polymorphonuclear leukocytes, but occasionally an increase in the number of lymphocytes; (4) turbidity of the fluid. These changes in the cerebrospinal fluid may be associated with the symptoms of meningitis, such as rigidity of the neck and the presence of Kernig's symptom. This reaction has received the name of meningitis sympathica by Plaut, Rehm and Schottmüller. The most frequent etiologic factor is inflammation of the ear, with or without mastoid sinus or labyrinth involvement, and in these conditions the presence of this syndrome is of great importance both from the point of view of the diagnosis and also of therapy.

AUTHOR'S SUMMARY.

THE SIGNIFICANCE OF THE PERICARDIUM IN RELATION TO SURGERY OF THE HEART. C. S. BECK and R. L. MOORE, *Arch. Surg.* **11**:550, 1925.

Of great importance in cardiac surgery is the prevention of adhesions between the heart and pericardium. Experiments were made to show that adhesions formed in response to mechanical trauma, hot salt solution, chemical irritants and infection. Fat transplants did not prevent the formation of adhesions. The protocols of the experiments are presented and the literature of cardiac surgery summarized.

N. ENZER.

EXPERIMENTAL HYDRONEPHROSIS. THE EFFECT OF CHANGES IN BLOOD PRESSURE AND IN BLOOD FLOW IN ITS RATE OF DEVELOPMENT. SPLANCHNOTOMY: INCREASED INTRARENAL BLOOD PRESSURE AND FLOW; DIURESIS. F. HINMAN and H. B. HEPLER, Arch. Surg. **11**:578, 1925.

In rabbits a complete unilateral ureteral obstruction with division of the splanchnic nerves on the same side does not produce a greater degree of hydronephrosis than simple ureteral obstruction, although splanchnotomy causes diuresis. The degree of hydronephrosis was proportional to the length of time the ureteral obstruction existed.

N. ENZER.

ACCESSORY LOBES OF THE LIVER. T. S. CULLEN, Arch. Surg. **11**:718, 1925.

Cullen reviews the literature on anomalies in size, position and lobulation of the liver, giving summaries of a large number of cases. He reports a case of an accessory lobe springing from the surface of the gallbladder possessing its own pedicle in which were branches of the hepatic artery, hepatic vein, portal vein and hepatic duct. There are only two similar cases on record. The article is well illustrated by Max Brödel, who contributes an explanation of the gross and microscopic picture of the specimen.

N. ENZER.

CONGENITAL DEFICIENCY OF THE PERICARDIUM. R. L. MOORE, Arch. Surg. **11**:765, 1925.

Sixty-four cases are on record, and forty-two are presented in summary in this article. In only one case was the defect right sided. In a large number adhesions existed between the heart, pleura, diaphragm and thoracic wall. These defects were associated with anomalies elsewhere in the body in six cases. A case of a right-sided defect in a dog is reported.

N. ENZER.

GASTROJEJUNOCOLIC FISTULAS. J. VERBRUGGE, Arch. Surg. **11**:790, 1925.

Two hundred and two cases were found in the literature, and fourteen new ones are added here in summary. In ninety-five the fistula resulted from a jejunal ulcer following gastro-enterostomy. The other 121 followed primary abdominal conditions, such as carcinoma, gastric ulcer, tuberculosis and trauma. The pathology and clinical features are described.

N. ENZER.

THE ORIGIN OF THE LEPRO CELL. JEAN OLIVER, J. Exper. Med. **43**:233, 1926.

By means of the method of vital staining, it is found that the lepra cell in rat leprosy is derived from the histiocyte.

From the similarity in morphology and function of the lepra cells in this condition and those of human leprosy, it seems likely that derivation of the cells in the two conditions is similar.

AUTHOR'S SUMMARY.

PRIMARY CONGENITAL DILATATION OF THE URETERS. J. S. EISENSTAEDT, J. Urol. **15**:21, 1926.

Congenital bilateral megalo-ureter may occur without demonstrable cause, and hence is called primary. The term primary megalo-ureter defines the condition better than congenital dilatation of the ureters. The cysto-

ureterograms and cystoscopic findings are characteristic, as observed in the two cases here reported. The mechanism underlying the development of this condition may be explained by embryologic considerations, probably as a deficiency in the development of the musculature of the ureters.

AUTHOR'S SUMMARY.

LEUKOPLAKIA OF THE BLADDER. OTTO J. WILHELMI, J. Urol. **15**:653, 1925.

Leukoplakia of the bladder is a rare condition of unknown etiology. A large variety of associated pathologic conditions are found: cystitis, calculi and kidney lesions. The symptoms are variable, with frequency, hematuria, pyuria and passage of epithelial cells most frequent. The cystoscope is the most reliable diagnostic aid. One sees irregularly shaped plaques, varying from white to gray, surrounded by normal or ulcerated mucous membrane.

B. R. LOVETT.

CARDIAC INFARCT AND CORONARY SCLEROSIS. G. WERLEY, Texas State J. Med. **21**:428, 1925.

The Clinical and Pathological Club of El Paso has performed 200 necropsies during the last two years, and in 25 per cent of the cases it found badly diseased hearts and aortas. Four per cent showed cardiac infarct or cardiac aneurysm. There were three cases of rupture of the left ventricle following coronary obstruction. In two specimens the right coronary artery was completely occluded, and in a third case the right coronary artery was almost closed at its orifice. There were five cases showing cardiac aneurysm due to syphilis. Werley says that it has been their experience that well marked lesions will be overlooked unless the examination is made in detail and includes opening of the coronaries, and histologic studies.

THE PATHOLOGY OF HYDRONEPHROSIS. H. P. WINSBURY WHITE, Brit. J. Surg. **13**:247, 1925.

White discusses the etiology and pathology of 159 cases of hydronephrosis collected from various sources. The hydronephroses resulting from calculus and tumors are not considered. In 85 per cent of the cases, the dilatation began at the pelvo-ureteral junction. In those occurring in fetal life or infancy, the dilatation was bilateral, and often involved one or both ureters, while in some there was a ureteral atresia. Attention is called to the cases in the literature of hydronephrosis associated with developmental malformations of the kidneys. The first manifestations of the acquired form of the disease occurred usually in the third decade of life. A pyelitis and evidences of chronic inflammation and partial obliteration of the ureter were frequently observed, and the presence of such changes in several very early cases of hydronephrosis suggests that ureteral narrowing from chronic inflammatory changes may be an important cause of the dilatation. There is no conclusive evidence that renal mobility is ever a cause of the condition, and traumatism of the ureter with obstruction from the contraction of a scar is seldom responsible. Eleven cases are described in which the hydronephrosis was complicated by the obstruction of the ureter by a blood vessel.

LAWRENCE JACQUES.

SOME UNUSUAL MANIFESTATIONS OF SPREAD BY IMPLANTATION OF PAPILLOMATA OF THE URINARY TRACT. B. C. MAYBURY and S. C. DYKE, *Brit. J. Surg.* **13**:377, 1925.

In one of the two cases described, a papilloma occurring in the renal pelvis became implanted in the wall of the resulting hydronephrosis. Removal of the affected kidney together with the tumor was followed by the rapid growth of a malignant tumor in the other kidney. In the second case, three "graft recurrences" arose in three separate places in the tissue of the abdominal wall following the removal of a vesical papilloma. The grafts were considered to have arisen from portions of the original tumor accidentally implanted at the first operation.

The first and second installments of an Atlas of Pathology are included as supplements to the July and October issues of the *British Journal of Surgery*. A beautifully illustrated series of bone tumors is presented.

LAWRENCE JACQUES.

TONSILS IN ENDOCARDITIS AND RHEUMATISM. K. A. HEIBERG, *Virchows Arch. f. path. Anat.* **257**:1, 1925.

No characteristic changes were found in the tonsils of patients suffering with chronic endocarditis or rheumatic fever.

O. T. SCHULTZ.

CELL CHANGES IN LYMPHADENOID TISSUE CULTURES. C. SHIOMI, *Virchows Arch. f. path. Anat.* **257**:714, 1925.

Shiomi reinvestigated Maximow's claim that in cultures of explanted lymphadenoid tissue treated with extract of bone marrow the reticulum cells form lymphocytes and the latter give rise to cells of the myelocyte series. In the absence of tissue extract Shiomi found that fibroblasts, reticulum cells and lymphocytes arose from preexisting cells of the same types. In the presence of extract of bone marrow, spleen or suprarenal, the various kinds of cells differentiate and hypertrophy and are less readily distinguished from each other. Under such conditions monocytes and macrophages arise from reticulum cells, and by fusion may form giant cells of foreign body type. The mobilized reticulum cells may give rise by metaplasia to large cells of lymphoid type which resemble megakaryocytes. The lymphoblasts do not come from the reticulum cells, but from cells of their own kind. The small lymphocytes do not become changed into polyblasts. Typical plasma cells are lymphocytic in origin, but pseudoplasma cells may arise from small proliferated reticulum cells. Reticulum cells of small and medium size may develop nonspecific cytoplasmic granules as the result of degeneration and may then resemble myelocytes and micromyelocytes.

O. T. SCHULTZ.

RHYTHMIC STRUCTURE OF HUMAN TISSUES. A. LAUCHE, *Virchows Arch. f. path. Anat.* **257**:751, 1925.

Lauche attempts an explantation of the peculiar bandlike arrangement of the nuclei which has been considered characteristic of neurinoma, but which may also be seen in leiomyoma, glioma, certain spindle cell melanoblastomas, and in smooth muscle. He believes the alternation of regularly placed bands of nuclei with nonnucleated cytoplasmic bands to be due to the occurrence of rhythmic periods of nuclear division which occur in tissues whose cells have a perivascular arrangement. Because of such an arrangement, the cells about

the vessel receive equal nourishment, so that all divide at the same time and the nuclei lie in the same plane. In smooth muscle the bandlike arrangement is the result of mechanical contraction changes.

O. T. SCHULTZ.

REGENERATION OF NERVE END-ORGANS IN SCARS OF THE SKIN. W. NASAROFF, *Virchows Arch. f. path. Anat.* **257**:777, 1925.

By means of the Golgi method Nasaroff studied the regeneration of sensory end-organs in healing wounds and in scars of the skin. Regeneration of the nerve fibrils occurs from the central end of the severed fibrils, growth being in the direction of the epithelium, which exerts a positive chemotaxis on the growing fibrils. Arrived at the epithelium, knoblike enlargements are formed on the fibrils; these constitute primitive end-organs. By folding and convolution more complicated end-organs, which simulate the Meissner bodies, are formed. Regeneration of Meissner bodies occurs also by ingrowth of the fibrils into the capsules of the preexisting bodies, the capsules being more resistant to the inflammatory process than the other skin structures. Vater-Paccini corpuscles and highly complex Meissner bodies were not seen in scars. Neurotization of the scar occurs more quickly in aseptic than in infected wounds and proceeds more rapidly in smaller scars than in larger ones. As the scar becomes more dense with age, some of the regenerated nerve fibrils and end-organs disappear.

O. T. SCHULTZ.

HERNIA OF THE BRAIN. ILSE FRANZ, *Frankfurt Ztschr. f. Path.* **33**:72, 1925.

Recklinghausen in 1870 for the first time described hernia of the cerebral substance through the dura in a patient dying of brain tumor. Franz has made a systematic investigation for hernia of the brain in 225 consecutive necropsies. In fifty-one cases, or 22.7 per cent, the condition was present. From a study of these cases it is concluded that hernia of the brain occurs in all ages and both sexes about equally. Microscopically, a differentiation could not be established between physiologic and pathologic hernia of the brain. The author believes that the condition is probably due to increasing and varying pressures, together with the weight of the brain itself, which causes the formation of tears and gaps in the dura.

ERNEST M. HALL.

TUMORS OF THE MEDIASTINUM. RICHARD BÖHMIG, *Frankfurt Ztschr. f. Path.* **33**:80, 1925.

A case of teratoma of the mediastinum and of the left side of the thorax is described in a 17 year old soldier. The tumor weighed 5,570 Gm. It was composed of connective tissue of embryonal and myxomatous character; in the stroma there were large cystic glandular spaces lined with columnar or cuboidal epithelium, and filled with gelatinous material. Hyaline and degenerated cartilage was also found. Innumerable large and small cystic spaces filled with blood were present.

ERNEST M. HALL.

EXPERIMENTAL STUDY ON INTOXICATION WITH DIAL AND VERONAL. K. SAMEJIMA, *Sc. Rep. Govt. Inst. Infect. Dis.* **3**:103, 1924.

Beginning with an account of the clinical manifestations of lethal doses of dial and barbital (veronal) in rabbits the writer goes on to a detailed description of the pathologic changes in these animals. These are as follows:

Central Nervous System: The changes consist essentially of degenerative changes, in the cortex most marked in the pyramidal cells of the third layer and the small nerve cells of the fourth and deeper layers. They are, in brief, obscuring of nuclear substance and frequent pyknosis; the Nissl bodies are largely disintegrated into finely granular material. The point of attachment of the neurofibril is swollen and sometimes disintegrated. Similar changes were noted in the cerebellar cortex and in the base where, however, they were less marked.

In the lung there is atelectasis followed by bronchopneumonia and terminating in widespread hepatization. Even in the atelectatic stage there is swelling and desquamation of the bronchial mucosa along with marked hyperemia of the alveolar wall, and some hemorrhage. In the bronchopneumonic stage the bronchioles and adjoining alveoli are filled with an exudate of pseudo-eosinophilic cells, eosinophils, mononuclears and red cells. No fibrin is observed. Attempts at demonstration of micro-organisms are unsuccessful. The widespread hepatization is the result of the spread of the localized bronchopneumonic foci.

Circulatory System: The principal change is acute myocardial degeneration, cloudy swelling and fatty degeneration. Glycogen content is markedly diminished. A considerable proportion of the hearts showed unilateral or bilateral dilatation.

Digestive System: In the stomach and intestines there is hyperemia of the mucosa; in the liver, fatty degeneration and the appearance of extensive vacuolization independent of this, the vacuoles containing neither fat nor glycogen—probably a dropsical degeneration. Necrosis, either of isolated liver cells or of entire lobules, was occasionally observed. In the pancreas fatty degeneration occurs, both in the gland cells proper and in the islands of Langerhans; the former is more conspicuous.

Hematopoietic Organs: In the bone marrow there is an inconstant hyperplasia of pseudo-eosinophilic cells. In the spleen there is usually atrophy with wrinkling of the capsule. This appears to occur at the expense of the follicles, the reticular tissue showing hyperplasia.

Urinary Reproductive Organs: In the kidney there are fatty degeneration and necrosis, most marked in the distal portion of the convoluted tubules and in the ascending limb of Henle. The bladder shows vascular congestion with distention of the wall. In the testis there is inconstant fatty degeneration of the epithelial cells.

Ductless Glands: The most marked changes are observed in the anterior lobe of the hypophysis where there is marked degeneration and in the thymus where there is cortical degeneration and swelling of reticular cells.

The writer explains the local changes as being largely the result of local excretion of the poisonous material. The marked circulatory disturbances which had been explained by Jacoby as due to the peripheral action of the drug, the writer believes to be principally of central origin.

H. E. EGGERS.

INVESTIGATIONS CONCERNING THE ORIGIN OF BLOOD PLATELETS. SVEND PETRI, *Acta path. et Microbiol. Scandinav.* 2:23, 1925.

The results presented are held by the author to refute Wright's hypothesis of the origin of platelets.

Pathologic Chemistry

BLOOD CHEMICAL FINDINGS DURING CONVULSIONS IN ACUTE HEMORRHAGIC NEPHRITIS. METCALF, MARGA and MORIARTY, *Am. J. Dis. Child.* **31**:65, 1926.

Convulsions in a child with acute hemorrhagic nephritis resulted in the following changes in the chemistry of the blood: The sugar content of the blood was greatly increased, a phenomenon which occurred more slowly in the spinal fluid. There was a rapid return of the blood sugar to normal following the convulsions, and a delayed fall of the spinal fluid sugar. The alkaline reserve decreased during convulsions (when no alkaline therapy was given). The phosphorus was unaffected by the convulsions, the constantly high value being attributed to the nephritis. The moderately elevated nonprotein nitrogen, due to the nephritis, was further unchanged except for a slight decrease following the convulsions. No definite change was found in the plasma chlorides or in the uric acid during convulsions.

AUTHORS' SUMMARY.

THE EFFECT OF THE ORAL ADMINISTRATION OF CALCIUM LACTATE AND THYROID EXTRACT ON THE CALCIUM CONTENT OF THE BLOOD SERUM IN PULMONARY TUBERCULOSIS. M. M. TEPLITZ, *Am. Rev. Tuberc.* **12**:222, 1925.

The oral administration of calcium lactate and thyroid extract to a tuberculous patient over a period of from six weeks to three months did not change the calcium content of the serum. Quiescent, mildly and moderately active patients had an average of 10.3 mg. of calcium in 100 cc. of serum, with variations from 9.1 to 11.5 mg.; a group of "markedly active and toxic patients" averaged 7.7 mg., with variations from 7.2 to 8.4.

MAX PINNER.

THE LOSS OF BASES IN DIURESIS AND ITS EFFECT UPON THE ALKALI RESERVE OF THE BLOOD. B. M. HENDRIX and D. B. CALVIN, *J. Biol. Chem.* **65**:197, 1925.

There is an abnormal loss of base into the urine and a marked fall in the alkali reserve following diuresis with urea, sodium nitrate, chloride or sulphate. The effect on the alkali reserve is more prolonged following diuresis with sodium chloride than with the nitrate. The loss of base is due to a lowered reabsorption from the overtaxed tubules.

ARTHUR LOCKE.

CHEMICAL FINDINGS IN THE BLOOD OF THE NORMAL DOG. R. I. HADEN and T. G. ORR, *J. Biol. Chem.* **65**:479, 1925.

The average nonprotein nitrogen content of the blood of the normal dog is 30.8 mg. per hundred cubic centimeters. The urea nitrogen is 11.7 mg., creatinine 1.5 mg., amino acid nitrogen 6.7 mg., sugar 82 mg., chlorides (as sodium chloride) 468 mg., and the carbon dioxide combining power of the plasma is 34.8 volumes per cent.

ARTHUR LOCKE.

INVESTIGATIONS ON THE MECHANISM OF THE ORIGIN OF LEUKOCYTOSIS AND LEUKOPENIA. E. WOLHEIM, *Klin. Wchnschr.* **4**:1960, 1925.

The changes in the distribution of the leukocytes in the blood stream are due to local changes in the distribution of electrolyte. A relative local increase

in the calcium or hydrogen ion concentration causes an increase in the local number of leukocytes. A relative increase of potassium or hydroxyl ions causes a decrease in the number of leukocytes.

ARTHUR LOCKE.

PIGMENTATION FROM HEMOGLOBIN. O. LUBARSCH, *Klin. Wchnschr.* 4:2137, 1925.

This is a detailed survey of the author's own investigations. The breakdown of the erythrocytes after extravasation occurs in two ways: The corpuscles become laked owing to the hypotonicity of the surrounding fluid, or they are ingested by the tissue cells and undergo intracellular decomposition. The product of extracellular destruction of hemoglobin is hematoidin, appearing as red-brown rhombic plates, as clusters of fine brown needles, as wavy threads, or as amorphous grains and splinters. It has no detectable iron content. The different forms of hematoidin are partly associated with different types of hemorrhage. Intracellular decomposition results in hemosiderin, which occurs in noncrystalline yellow-brown grains and clumps and contains iron. It is probably an iron hydroxide. The original article should be consulted for the thorough discussion of the pathology of hemoglobinogenic pigmentation.

ARTHUR LOCKE.

THE ACETONE-BODY CONTENT OF THE BLOOD IN THE TOXEMIA OF PREGNANCY. O. BOKELMANN and A. BOCK, *Klin. Wchnschr.* 4:2158, 1925.

The blood of normal, nonpregnant persons contains an average of 2.985 mg. per cent of acetone bodies. This figure is increased to 3.977 mg. per cent during normal pregnancy, to 5.4 mg. per cent with albuminuria, 6.5 mg. per cent with eclampsia, 6.665 mg. per cent in the pre-eclamptic state, and to 7.5 mg. per cent with severe toxemia. Especially high values are found with hyperemesis. There is no parallel between the acetone-body content of the blood and the quantity of protein eliminated in the urine.

ARTHUR LOCKE.

THE OXIDATIVE FERMENTS OF THE LEUKOCYTES. H. MIELKE, *Klin. Wchnschr.* 4:2201, 1925.

A study was made of the response of the different groups of leukocytes to the Graham benzidine reaction. No conclusions are drawn.

ARTHUR LOCKE.

THE BLOOD-SUGAR AND CARCINOMA. F. SILBERSTEIN, J. FREUD and T. RÉVÉSZ, *Klin. Wchnschr.* 4:2252, 1925.

The action of insulin on persons with inoperable carcinoma is somewhat delayed and protracted.

ARTHUR LOCKE.

THE SIGNIFICANCE OF THE CHEMICAL COMPOSITION OF ORGANS IN PATHOLOGICAL CHANGES. G. HOPPE-SEYLER, München. *med. Wchnschr.* 72:1321, 1925.

A quantitative determination of the most important cell constituents is a good measure for the serviceability of an organ. Deviation from the normal indicates an impairment of function. Examples are given.

ARTHUR LOCKE.

THE OCCURRENCE OF PHENOL IN NORMAL BLOOD, ITS QUALITATIVE AND QUANTITATIVE DETERMINATION BY THE MILLON REACTION, AND REMARKABLE BLOOD-PHENOL VALUES IN DISEASE, ESPECIALLY IN PERNICIOUS ANEMIA. E. BECHER, S. LITZNER and W. TÄGLICH, München. med. Wchnschr. **72**:1676, 1925.

The phenol occurs in a bound condition and is freed by acid hydrolysis before the determination. Pernicious anemia is indicated by increased phenol values and the presence of some free phenol. There are increased phenol values in renal insufficiency which parallel the clinical symptoms of true uremia.

ARTHUR LOCKE.

BILIRUBINEMIA IN PREGNANCY. E. HERRMANN and F. KORNFELD, Zentralbl. f. Gynäk. **49**:2225, 1925.

With the oxidation method an increased bilirubinemia was found in all the pregnant women examined. The reaction was stronger in the first months. Women with pernicious vomiting had high concentrations of bilirubin. The increase was not constant in eclampsia.

Microbiology and Parasitology

THE EFFECT OF TEMPERATURE ON PROTOZOAN AND METAZOAN PARASITES, AND THE APPLICATION OF INTRA-INTESTINAL THERMAL THERAPY IN PARASITIC AND OTHER AFFECTIONS OF THE INTESTINE. D. DERIVAS, Am. J. Trop. Med. **6**:47, 1926.

Protozoan and metazoan parasites are killed by heat at from 45 to 47 C. in a few minutes, and colonic washing with salt solution seems to be of advantage in treatment of amebic dysentery and of parasitic infestation of the large intestine. Similarly, washing through the duodenal tube may be of advantage in giardiasis and other parasitic infestations of the small intestine.

STUDIES ON TRICHOMONAS BUCCALIS. MARY JANE HOGUE, Am. J. Trop. Med. **6**:75, 1926.

Trichomonas buccalis has been found only in the mouths of persons with purulent infection about the teeth. The parasite grows well in acid and alkaline mediums and is killed by heat at 45 C. for five minutes.

STUDIES ON RESPIRATORY DISEASES. ELECTROPHORETIC POTENTIAL, VIRULENCE AND SERUM AGGLUTINATION WITH SINGLE CELL CULTURES OF VARIANTS OF TYPE 1 PNEUMOCOCCI. I. S. FALK and M. A. JACOBSON, J. Infect. Dis. **37**:507, 1925.

Of a total of 15 single cell strains isolated from Blake and Trask's A, B and C cultures of pneumococci (A=type 1; B and C are variant strains obtained from A by growth in the presence of homologous antiserum) one (A1) showed evidences of contamination. Experiments with the remaining 14 (5 from A, 5 from B, 4 from C) and with the parent strains demonstrate that each of the single cell strains is indistinguishable from the parent strain from which it was derived with respect to electrophoretic potential, virulence for white mice and serum agglutination.

The parent strains (originally received from Dr. F. G. Blake Feb. 25, 1924) and the single cell strains (isolated between Dec. 27, 1924, and March 1, 1925)

have been carried in stock on blood-agar slants through a large number of generations. At the time of this writing there have been no evidences of spontaneous changes in the parent strains (A orig., B orig., C orig.) or in the single cell strains. So far as concerns the characteristics studied, each breeds true.

It is not our intent to enter into a discussion of the significance of the data reported here for the concepts of genetics in forms showing uniparental inheritance until experiments now in progress have been completed. It is pertinent merely to reiterate the significance of the finding illustrated above that a single cell strain of the C variant reverts to A on passage through a mouse.

AUTHORS' SUMMARY.

THE EFFECT OF HYDROGEN ION CONCENTRATION ON CERTAIN ANTIGENIC PROPERTIES OF CLOSTRIDIUM BOTULINUM. I. S. FALK and F. POWDERMAKER, J. Infect. Dis. **37**:514, 1925.

Using methods essentially like those of Starin and Dack, we have succeeded in producing in rabbits potent agglutinating serums for *Cl. botulinum*.

These serums show heterologous as well as homologous agglutinating potencies for strains of the antitoxic A and B types.

The serologic differences between the A and B types appear to be of a quantitative rather than qualitative nature.

The addition of acid (to $pH=2$) or of alkali (to $pH=10$) to the antigen suspensions or the separate injection into the peritoneal cavity of an equivalent quantity of acid or alkali effects the following changes: an increase in the agglutinating titer of an anti-A serum for type A organisms; a reduction in the titer of an anti-B serum for type B organisms; a reduction (in 18 of 24 serums) in the titer of an anti-A or an anti-B serum for the heterologous type of organism.

AUTHORS' SUMMARY.

INTRA-UTERINE INJECTION OF ACID-FAST BACILLI INTO THE GUINEA-PIG. YUN CHAN SUN, O. ISHII and LEO LOEB, J. Infect. Dis. **37**:528, 1925.

The principal differences between the intra-uterine injection of nonvirulent, acid-fast bacilli or virulent tubercle bacilli, and the generally used subcutaneous, intraperitoneal or intravenous inoculation is that the former is followed by extensive, localized, well encapsulated lesions at the place of inoculation in which the bacilli persist noncontaminated in the exudate, while in the latter such persistent localized and encapsulated lesions are not found. Thus it is possible to produce notable localized chronic lesions with acid-fast bacilli which otherwise would call forth only transitory elusive changes. Intra-uterine as well as subcutaneous injections of virulent tubercle bacilli are followed equally by generalized tuberculosis. Notwithstanding the great difference in the general effects which follow intra-uterine injection of the virulent and nonvirulent acid-fast bacilli, both micro-organisms persist in the uterine cavity approximately equally well, and both are taken up by leukocytes; but in the nonvirulent bacilli the lesions remain localized, while in the virulent bacilli they extend to other organs. It may be suggested that this method might prove of interest in the study of processes of immunity as well as of certain other virulent micro-organisms the fate of which after subcutaneous, intra-peritoneal or intravenous injection is difficult to establish.

AUTHORS' SUMMARY.

NATURE OF THE TOXIC SUBSTANCES PRODUCED BY *B. SUIPESTIFER*. E. E. ECKER and M. L. RICHARDSON, J. Infect. Dis. **37**:538, 1925.

Young cultures of *B. suipestifer* grown in 2 per cent Witte peptone broth $pH \pm 7$, on solid mediums, and in a simple synthetic medium, produce a poison of unknown nature, which on intravenous injection into rabbits causes a characteristic series of acute changes after a definite incubation period of at least forty minutes.

This substance appears to have some antigenic properties, but comparatively large doses of immune serum (5 cc.) are necessary to afford protection to rabbits. When the serum is given immediately (in from 10 to 15 minutes) prior to the dose of the poison itself, protection is afforded.

AUTHORS' SUMMARY.

PRODUCTION OF TOXIC SUBSTANCES IN YOUNG CULTURES OF SINGLE CELL STRAINS OF *B. PARATYPHOSUS* B. E. E. ECKER and EMERSON MEGRAIL, J. Infect. Dis. **37**:546, 1925.

Berkefeld N filtrates of 2 per cent Witte peptone veal infusion broth cultures of five single cell strains from each of two cultures of *B. paratyphosus* B, 180 and 185, injected intravenously into rabbits proved to be as toxic as the filtrates of the parent cultures. Boiling of the filtrates for three minutes in a water-bath did not disclose a diminished toxicity, as compared with the boiled filtrates of the original cultures. No significant differences in cultural characteristics were noted between the single cell and parent strains.

AUTHORS' SUMMARY.

AN ATYPICAL WEIL-FELIX REACTION. RUTH GILBERT and MARION COLEMAN, J. Infect. Dis. **37**:559, 1925.

A case is described in which no definite diagnosis was made, the following diseases being, in turn, considered and rejected: grip, typhoid, Brill's disease, tick-bite fever, Rocky Mountain spotted fever. Both before and after inactivation by heating at 62 C. the patient's serum agglutinated *B. proteus* $\times 19$ in dilutions up to 1:1,600, whereas serum from cases known to be typhus fever lost the agglutinins for *B. proteus* $\times 19$ at a point between 54 and 56 C. In immune rabbit serum the agglutinins were not destroyed until between 70 and 75 C. was reached. These results indicate the desirability of determining the relative thermolability of the agglutinins in serum from suspected cases of typhus fever.

AUTHORS' SUMMARY.

STUDIES OF EXPERIMENTAL RICKETS. I. THE OCCURRENCE OF RICKETS IN YOUNG RABBITS BORN OF MOTHERS INFECTED WITH *SCHISTOSOMUM JAPONICUM*. R. KAWANURA and Y. KASAMA, J. Exper. M. **42**:793, 1925.

Young rabbits born of mothers afflicted with *Schistosomum japonicum* develop typical rickets. Rickets can also be produced by infecting the young, healthy rabbits with the same parasite. It is natural to suppose that the rachitic changes are caused by the parasite itself. Since, however, a similar disease can be produced in the offspring, when the mother is fed on egg yolk, the causation is not limited to the action of this parasitic toxin alone.

The toxin of *Schistosoma* may disturb the calcium and phosphorus metabolism of bone in young animals, especially in the period of vigorous growth;

that is, from twenty to forty days after birth of the rabbits; or it may exhaust some element important in the calcium and phosphorus metabolism, such as vitamin A or D. The fact that exhaustion of the antirachitic factor in the mother causes rickets in the young, as Grant (1924) showed, and that certain low grade infections can exhaust vitamin B as shown by Wedgewood (1924), is in line with this conception.

It may be added here that most investigations on rickets have been carried out on rats and dogs. A simple and excellent way of producing rickets in rabbits by dietary deficiency has been found, which will be reported elsewhere.

AUTHORS' SUMMARY.

THE PROBLEM OF THE ETIOLOGY OF HERPES ZOSTER. RUFUS COLE and ANN G. KUTTNER, J. Exper. M. **42**:799, 1925.

Attempts to inoculate rabbits, guinea-pigs and monkeys with material obtained from nine cases of herpes zoster have proved unsuccessful.

STUDIES ON THE BACTERIOPHAGE OF D'HERELLE. IV. CONCERNING THE ONENESS OF THE BACTERIOPHAGE. JACQUES J. BRONFENBRENNER and CHARLES KORB, J. Exper. M. **42**:821, 1925.

Lytic filtrates, active against *Bacillus dysenteriae* Shiga, *Bacillus coli*, *Bacillus pestis-caviae*, and staphylococcus, respectively, proved to be differently affected by changes in hydrogen ion concentration.

Antistaphylococcus lysin was the least resistant of the four, showing deterioration in three hours at 7 C. beyond the zone of hydrogen ion concentration limited by $C_h = 6.3 \times 10^{-3}$ and $C_h = 1.6 \times 10^{-3}$. Under the same conditions, the zone of resistance of anticoli filtrate lay between $C_h = 2.7 \times 10^{-3}$ and $C_h = 2.5 \times 10^{-11}$, and that of anti-Shiga between $C_h = 1.7 \times 10^{-4}$ and $C_h = 1.3 \times 10^{-11}$. Antipestis caviae filtrate was most resistant of the four, retaining its full activity in the zone from $C_h = 1 \times 10^{-3}$ to $C_h = 3.5 \times 10^{-12}$.

The fact that these differences in individual resistance persisted notwithstanding the repeated passage of lytic filtrates through cultures of bacteria other than those against which they were primarily active, seems to offer evidence in favor of a multiplicity of bacteriophages.

AUTHORS' SUMMARY.

STUDIES OF LEPTOSPIRA HEBDOMADIS. M. KOSHINA, S. SCIOZAWA and K. KITAYAMA, J. Exper. M. **42**:873, 1925.

From the results of etiologic study of the disease known as akiyami which prevails in the Shida district of Shizuoka province, it is concluded that:

Akiyami is an infectious disease caused by a leptospira.

The leptospira causing akiyami is difficult to differentiate morphologically from *Leptospira icterohaemorrhagiae* and *Leptospira hebdomadis*.

The strains of leptospira isolated from cases of akiyami are of two types. One type, isolated from three of the sixteen cases, is highly virulent for guinea-pigs, and is serologically distinct from *Leptospira icterohaemorrhagiae* and *Leptospira hebdomadis*; we have called this the A type. The type obtained from the other cases is less virulent for guinea-pigs and is serologically identical with *Leptospira hebdomadis*; we have called this the B type.

The field mouse (*Microtus montebelli*), which harbors *Leptospira hebdomadis*, has also been found to harbor the A type of akiyami.

AUTHORS' SUMMARY.

STUDIES ON BRUCELLA MELITENSIS. III. EXPERIMENTAL ABORTION IN A COW PRODUCED BY INOCULATION WITH A HUMAN STRAIN. ALICE C. EVANS, Hyg. Lab. Bull. **143**:33, 1925.

Experimental abortion was induced in a pregnant heifer by inoculation with a culture of *Br. melitensis*, variety melitensis A, from a human case of Malta fever, and the inoculating strain was recovered from the fetus and the colostrum.

AUTHOR'S SUMMARY.

STUDIES ON BRUCELLA MELITENSIS. V. HOGS AS A POSSIBLE SOURCE OF HUMAN INFECTION. ALICE C. EVANS, Hyg. Lab. Bull. **143**:57, 1925.

Considering the exalted virulence of porcine strains of *Br. melitensis*, the prevalence of swine infection, the susceptibility to Malta fever of butchers in France, and the histories of the two cases here reported, it would appear that watchfulness for Malta fever among butchers and others who handle hogs or hog carcasses in this country might reveal that the disease is more prevalent than is generally suspected.

AUTHOR'S SUMMARY.

ROCKY MOUNTAIN SPOTTED FEVER IN INDIANA: REPORT OF A CASE. C. R. LABIER, Ind. State Med. Ass'n J. **18**:418, 1925.

LaBier's case is of interest since it occurred in Terre Haute, Ind., in a girl who had not been out of the immediate vicinity of the city. The clinical course was typical. While playing in a pile of gravel the child had been bitten by a brown and black bug the size of a "butter bean." On examination, a lesion was found in the scalp behind the right ear, and in a short time the lymph glands behind the ear were enlarged and tender. Constitutional symptoms set in three days later—drowsiness, headache, fever and a skin rash. One outstanding symptom was prevalent throughout the course of the disease, a pronounced sleepy condition. The child could be aroused and immediately would fall back to sleep, when she would have to be aroused again for food, liquids and medication. This was quite marked during the first three weeks of illness.

ETIOLOGY OF TYPHUS. P. HANDUROY, Presse méd. **57**:356, 1925.

The question is raised whether *Rickettsia prowazeki* and *Proteus X* may not be different forms of the same filtrable virus.

LAMBLIASIS OF THE GALLBLADDER. LABBÉ, NEPVEUX and GAVRILA, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1505, 1925.

In eighty-five intubations of the duodenum, for different affections, Labbé, Nepveux and Gavrila found *Giardia lamblia* in the gallbladder in 8.2 per cent. A rebellious dyspepsia and consecutive malnutrition were the predominant manifestations. The dyspepsia was chiefly of intestinal origin, characterized by an intermittent or permanent diarrhea. Dysentery was revealed in the history of most of the patients, preceding the lambliasis by thirty-seven years in one of them. Later appeared the involvement of the duodenum, or directly of the gallbladder. The different stages of the disease are entailed by the upward moving of *Giardia intestinalis*. In the advanced stage, the parasite may be absent from the stools and may be found exclusively in the bile of the gallbladder. No treatment, used to date, has displayed any efficacy.

OBSERVATIONS ON THE WHITE CELLS OF THE BLOOD IN RECURRENT FEVER.
E. V. KARTACHEFF, *Ann. de l'Inst. Pasteur* **39**:969, 1925.

The number of polymorphonuclear leukocytes fall during the course of the disease with a rapid fall at the crisis, while the monocytes remain high even after the crisis. Monocytes and large mononuclear cells containing vacuoles are more phagocytic than polymorphonuclear leukocytes.

G. B. RHODES.

ECHINOCOCCUS DISEASE OF LOWER ANIMALS. H.-J. ARNDT, *Virchows Arch. f. path. Anat.* **257**:512, 1925.

This is a study of glycogen and cholesterol deposition in echinococcus cysts of lower animals.

O. T. SCHULTZ.

MYCOTIC GRANULOMA OF THE LABIUM MAJUS. E. RISAK, *Virchows Arch. f. path. Anat.* **257**:744, 1925.

Risak describes a tumor-like enlargement of the labium majus composed of granulation tissue, in which were multiple abscesses. In the latter were peculiar structures believed to be fungi belonging to myxomycetes.

O. T. SCHULTZ.

PRESENCE OF CAUSE OF WEIL'S DISEASE (SPIROCHAETA ICTEROHEMORRHAGICA) AND OF RAT-BITE FEVER (SP. MORSUS-MURIS) IN VIENNA RATS. I. TAKAKI, *Wien. klin. Wchnschr.* **38**:1231, 1925.

Examinations of the organs of normal rats with dark field and stained (Giesmsa) preparations, and by inoculation into guinea-pigs, also into mice for the rat-bite fever studies, revealed that the rats in Vienna are spirochete carriers. Reports from other cities and countries state that in some places as many as 75 per cent of the rats are infected. For epidemiologic reasons and for national economy, therefore, the extermination of rats is recommended.

E. B. PERRY.

AMEBIC INFECTION OF THE URINARY TRACT AND AMEBIC CYSTITIS. M. PETZETAKIS, *Wien. klin. Wchnschr.* **38**:1310, 1925.

Reference is made to a previous report of an amebic nephritis, and two cases of cystitis are described, both with amebas in the urine, but only one with amebas demonstrated in the stools. Cure of the cystitis by the use of emetin is considered indicative of the pathogenicity of the ameba. Amebiasis is discussed as a general infection, with an amebemia and many localizations, of which the one in the intestine with its resulting dysentery is the most easily recognizable. Because of the infectious nature of dried feces, thorough disinfection of all excretions is urged as the chief prophylactic measure. The recent reports of amebic infections of the urinary tract by Warthin and by Hines are not mentioned.

THE SIGNIFICANCE OF CLIMATIC ALLERGIES (MIASMAS) IN THE ETIOLOGY OF ALLERGIC DISEASES. W. STORM VAN LEEUWEN, Z. BIEN and H. VAREKAMP, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **43**:490, 1925.

The air of Rotterdam was filtered through cotton, and the filter then extracted with physiologic sodium chloride. This extract produced attacks

in asthmatic persons. It differed in certain respects (lack of local reaction after subcutaneous infection) from other antigens which produced asthma. The authors believe this is convincing proof that the effects of certain climates are due to the presence of substances in the air, which are inhaled.

JEAN OLIVER.

Immunology

COMPLEMENT FIXATION IN TUBERCULOSIS. IV. STUDIES ON THE NATURE OF THE ANTIBODY. M. PINNER, *Am. Rec. Tuberc.* **12**:233, 1925.

Serum of tuberculous patients with positive complement fixation was digested with trypsin and dialyzed simultaneously until chemically free from proteins and protein split products; these preparations still contained complement-fixing antibodies.

The complement-fixing tuberculous antibodies are therefore not of the nature of globulins. They are either lipoids or proteins which are not broken up by the action of trypsin, that is, proteins with the CO-NH linkage.

In accordance with previous results, it has been demonstrated that the complement-fixing antibodies have apparently no quantitative or qualitative relation to the ethylbutyrases ("lipases"). True lipases with a specific action on tubercle bacillus lipoids could not be detected in serum with complement-fixing qualities.

That serum of tuberculous patients which twenty-four hours after the withdrawal of the blood gives a negative complement-fixation test, and becomes positive after standing for a week or more (Wedel), is not specific for tuberculosis; the same occurrence is observed, although in a much smaller percentage, in serum of undoubtedly nontuberculous persons.

Complement-fixing antibodies may readily be destroyed by ether. Any procedure which uses ether extraction is therefore to be excluded from examinations for complement-fixing antibodies.

S. A. LEVINSON.

DETOXICATION OF BACTERIAL VACCINES BY FORMALDEHYDE. W. B. WHERRY and J. A. BOWEN, *J. Infect. Dis.* **37**:520, 1925.

Incubation of *B. dysenteriae* Shiga in solutions containing 0.04 of 1 per cent formaldehyde for one week detoxicates the antigens. Large doses may be injected into rabbits without harm and potent agglutinating serum formed. Rabbits immunized in this way are resistant to doses of living bacilli which will kill controls. The results of preliminary experiments with typhoid bacilli indicate that treatment of the bacilli with formaldehyde materially reduces their toxicity for human beings.

AUTHORS' SUMMARY.

SEPARATION OF A SOLUBLE SPECIFIC SUBSTANCE FROM HEMOLYTIC STREPTOCOCCI. EDWIN F. HIRSCH, *J. Infect. Dis.* **37**:523, 1925.

A soluble specific substance has been extracted from hemolytic streptococci. The chemical reactions of this substance resemble those of similar substances prepared from many bacteria by other investigators. Solutions of this substance give precipitin reactions in high dilution with antistreptococcus serums, and with the serum of rabbits injected with the substance.

AUTHOR'S SUMMARY.

ANTIBODY RESPONSE TO LARGE AND SMALL DOSES OF MULTIPLE AND SINGLE ANTIGENS, AND RESTIMULATION OF SPECIFIC ANTIBODY FORMATION BY HETEROLOGOUS ANTIGENS. MARION CORRIGAN, J. Infect. Dis. **37**:549, 1925.

Polyvalent bacillary antigens in large or in small doses induced practically as high an agglutinin titer for each of their constituent organisms as did monovalent bacillary antigens. Polyvalent streptococcic antigens produced a lower titer than did monovalent streptococcic antigens. It was observed that small doses of polyvalent streptococcic antigen were more effective than large doses in the production of agglutinins.

The reinjection into formerly immunized animals retaining no antibodies in the blood caused a slight recurrence of antibodies for the original antigen accompanied by a normal production of antibodies for the bacteria used in the reinjection. The recurrence of antibodies seemed to be independent of the variety of bacteria subsequently injected.

The results of the reinjection into animals retaining antibodies in the blood varied. Reinjection in some cases caused a rise in the titer of the original antibodies, and on one occasion did not hinder the normal decrease of the original antibodies. Here again the reformation of the original antibodies did not depend on the variety of bacteria subsequently injected. The titer of the antibodies for the organism used in reinjection was comparable to that induced by injection into normal rabbits.

AUTHOR'S SUMMARY.

SEROLOGICAL STUDIES ON THE BLOOD OF THE PRIMATES. II. THE BLOOD GROUPS IN ANTHROPOID APES. K. LANDSTEINER and C. PHILIP MILLER, J. Exper. M. **42**:853, 1925.

Blood specimens of twenty-one anthropoid apes have been examined serologically. It was found possible to assign each to one of the four human blood groups.

The iso-agglutinogens of the anthropoids were found to be identical with those of human blood. These same factors could not be demonstrated in the blood of the lower monkeys.

In the blood of the fourteen chimpanzees examined, only iso-agglutinin A has been found, whereas both A and B were present in the blood of the six orangutans.

The significance of these findings for the knowledge of the human blood group is discussed.

AUTHORS' SUMMARY.

SEROLOGICAL STUDIES ON THE BLOOD OF THE PRIMATES. III. DISTRIBUTION OF SEROLOGICAL FACTORS RELATED TO HUMAN ISO-AGGLUTINOGENS IN THE BLOOD OF LOWER MONKEYS. K. LANDSTEINER and C. PHILIP MILLER, J. Exper. M. **42**:863, 1925.

Serologic studies on blood specimens of thirty-six species of lower monkeys have shown that there exists a correspondence between the distribution of a certain hemagglutinin and the place of the species in the zoological system.

In twelve species of seven genera of *Platyrrhina* (new world monkeys) and six species of the genus *Lemur* a factor similar to the human iso-agglutinin B was present; in eighteen species of four genera of *Cercopithecidae* (old world monkeys) it was absent, although the latter are more closely related to man than the former.

It would seem from our findings that a genus, perhaps even a family, of animals may be characterized by a special serologic factor. The factor found in the lower monkeys is not identical with the one existing in the erythrocytes of the anthropoid apes and man.

AUTHORS' SUMMARY.

EXPERIENCES WITH MEINICKE'S TURBIDITY REACTION (TRÜBUNGSREAKTION) FOR SYPHILIS IN MORE THAN 700 SANITARIUM PATIENTS. E. HAGER, *Ztschr. f. Tuberk.* **43**:477, 1925.

This reaction proved to be specific, and was apparently not influenced by febrile tuberculosis. The author believes with Meinicke that one obtains the best sero-diagnostic results in syphilitic patients by running the Wassermann and Meinicke reaction on each serum. About 4 per cent of the patients examined were found to be syphilitic.

MAX PINNER.

EXPERIMENTS CONCERNING THE RELATIONSHIP BETWEEN IMMUNITY AND CHOLESTEROL METABOLISM. RICHARD PRIGGE, *Ztschr. f. Hyg. u. Infektionskr.* **105**:299, 1925.

The author concludes from his experiments regarding the formation of hemolysins in rabbits that our knowledge of the factors influencing cholesterol metabolism is too imperfect to gage the progress of an immunization by a determination of the cholesterol contents of the serum.

W. OPHÜLS.

WASSERMANN REACTION AND THE BLOOD GROUPS. O. STRASZYNSKI, *Klin. Wchnschr.* **4**:1960, 1925.

Straszyński confirms the observation that in Poland the individuals of the Group O (Jansky I) lose their positive Wassermann reaction sooner than Groups A (II), B (III) and especially A B (IV). The ratio was 1:1.63:2:2.4. It seems therefore that the rapidity of the disappearance of the Wassermann reaction under treatment is a constitutional character which is in correlation with the blood group. He emphasizes that this does not mean as yet that the curability is parallel.

ON THE RESULT OF THE WASSERMANN REACTION WITHIN DIFFERENT BLOOD GROUPS DURING THE TREATMENT OF SYPHILIS. A. STRASZYNSKI, *Klin. Wchnschr.* **4**:1962, 1925.

The speed with which the Wassermann reaction disappears under the influence of antisyphilitic treatment is a constitutional property correlated with the blood group of the patient.

ARTHUR LOCKE.

CONTRIBUTIONS TO THE STUDY OF THE PATHOGENESIS OF ANAPHYLACTIC SHOCK AND OF OTHER PROCESSES AKIN TO ANAPHYLAXIS. I. KRITSCHESKY and X. FRIDE, *Arb. a. d. Microbiol. Inst. d. Volksunterrichtskommissariats* **1**:133, 1924.

Anatomic lesions found after death by anaphylaxis as well as kindred types of death—peptone poisoning, cellular anaphylaxis, poisoning by hemolytic serum, by primarily toxic serum, etc.—are identical both qualitatively and quantitatively. In all of these the toxic process consists essentially of alteration of degree of dispersion of cellular colloids. The lesions of parenchymatous organs

and of muscle are to be viewed as resulting from diminished dispersion of the ganglion cells of increased dispersion. Hemorrhage and edema result from similar changes in the endothelial cells.

H. E. EGGERS.

CELLULAR ANAPHYLAXIS. I. KRITSCHESKY and X. FRIDE, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskommissariats 1:161, 1924.

Cellular anaphylaxis to erythrocytes can be readily induced in the dog, all the animals experimented on having manifested the phenomenon. In most cases one sensitizing dose is sufficient; rarely two are required. In some animals only one shock is obtainable. In others shock follows each (late) injection. Hemolysin production is proportionate to the degree of shock. Symptoms of shock in this cellular anaphylaxis are identical with those of serum anaphylaxis.

H. E. EGGERS.

CELLULAR ANAPHYLAXIS. I. KRITSCHESKY and O. DUKELSKY, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskommissariats 1:192, 1924.

The possibility of producing both active and cellular anaphylaxis in the dog in the same circumstances which evoke passive serum anaphylaxis in the guinea-pig, and the doubtfully established cellular anaphylaxis in rabbits, show beyond doubt that cellular anaphylaxis is as real a phenomenon as serum anaphylaxis.

H. E. EGGERS.

Tumors

THE EFFECT OF OPERATIVE INTERFERENCE WITH THE CERVICAL SYMPATHETIC NERVOUS SYSTEM UPON THE GROWTH AND MALIGNANCY OF A TRANSPLANTABLE NEOPLASM OF THE RABBIT. LOUISE PEARCE and CHESTER M. VAN ALLEN, J. Exper. Med. 42:431, 1925.

The effect of the removal of the complete cervical sympathetic nervous system, of both superior and of both inferior cervical ganglions, and of a small portion of the cervical sympathetic nerve in the rabbit was studied in relation to the character of a malignant disease induced by a transplantable neoplasm.

It was found that the general character of the disease which developed in the operated groups of animals was more severe than that of a similar sized control group. Comparisons of the mortality rate in the several groups, of the animal incidence of metastases, of the number of metastatic foci and of the distribution of these secondary growths all showed this to be the case. There appeared, furthermore, to be differences in malignancy among the operated groups themselves. The most severe disease occurred in the group in which a portion of the sympathetic nerve only was removed (sympathotomy); that in the complete sympathectomy and superior sympathectomy groups was slightly less malignant and that in the inferior group was much less so.

These results have been interpreted as being due to a less effective animal resistance, the mechanism of which has been interfered with in some way by the interference with the sympathetic nerves. The reasons for the difference in malignancy exhibited by the several operated groups are undetermined. A tentative explanation is suggested on the basis of coordinating favorable or deleterious functions subserved by the cervical sympathetic nervous system.

AUTHORS' SUMMARY.

GROWTH AND PERSISTENCE OF FILTERABLE VIRUSES IN A TRANSPLANTABLE RABBIT NEOPLASM. THOMAS M. RIVERS AND LOUISE PEARCE, *J. Exper. Med.* **42**: 523, 1925.

Virus 3 and vaccine virus multiply in a transplantable rabbit tumor of epithelial origin; they are carried along with the tumor through an indefinite number of transplants, and despite an immunity developed by the rabbit host, survive longer in the tumor than when injected into the testicles of normal rabbits.

AUTHORS' SUMMARY.

EXPERIMENTAL CANCER IN WHITE MICE. I. BARTOZEK, *Trav. d'Inst. d'anat. path. d. Univ. de Pologne* **1**:387, 1925.

The author painted white mice with tar. In the first month, he noticed thickening of the epithelium, with growth of the subcutaneous connective tissue, increase in fibroblasts and elastic tissue. In the second month, there was further growth of the epithelium and of the connective tissue, with hyaline degeneration and multiplication of the elastic fibers. In the third month, warts appeared, and tongue-like growths of epithelium extended down into the connective tissue. Between these the elastic fibers were broken up and disappearing. By the fourth month, there were cancerous new growths in all of the animals. Microscopically, the muscle and cartilage of the ear was invaded by atypical epithelial cells. The growths had reached a size of 2.5 by 1.5 cm., and the nutrition of the animals was impaired.

B. R. LOVETT.

PATHOLOGIC ANATOMY OF PRIMARY TUMORS OF THE HEART, WITH CLINICAL REMARKS. W. NOWICKI, *Trav. d'Inst. d'anat. path. d. Univ. de Pologne* **1**:444, 1925.

The lack of well-defined symptoms of primary tumors of the heart is a cause of the neglect of this subject by clinicians. The author saw four tumors at necropsy that were not diagnosed.

The first was in a 70 year old woman, in whom the diagnosis of atherosclerosis with cardiac hypertrophy and venous congestion was made. In the left ventricle, arising from the septum, a papilloma was found, consisting of hyaline connective tissue covered by a single layer of endothelium. It caused no symptoms referable to its location, being too far from the aortic orifice to cause obstruction.

The second was in a 29 year old woman, who had had palpitation, pain in the chest, bloody sputum and dyspnea for six years. She died of general cardiac weakness. An egg-sized myxomatous tumor was found in the left auricle, blocking the pulmonary vein opening.

The third case was that of a 62 year old woman, in whom necropsy revealed carcinoma of the stomach with liver metastases. A myxoma the size of a walnut was found in the left auricle, arising from the fold covering the foramen ovale and nearly closing the opening of the pulmonary vein. The structure and lack of other changes in the heart distinguish these tumors from organized thrombi.

The fourth instance occurred in a woman, aged 40, who had had cough, bloody sputum, and dyspnea for four weeks. Clinically, cardiac hypertrophy, with murmurs and friction rub were found. She died of heart failure. A tumor the size of an orange completely filled the left auricle, blocking both the pulmonary vein opening and the auriculo-ventricular orifice. It was a spindle cell sarcoma, arising probably from the fold covering the foramen ovale.

From these cases one can conclude that slowly developing signs of cardiac weakness, without other demonstrable cause, and unusually large size of one chamber of the heart as compared with the others, are points in the diagnosis of cardiac tumors. Evidently the tumor can alter its position with changes in the position of the patient and direction of the blood flow. Probably murmurs can appear and disappear as the mass blocks one of the openings or falls away from it. Disturbances in the circulation of the blood that involve only one side of the heart speak for tumors.

B. R. LOVETT.

PRIMARY MALIGNANT EPITHELIAL TUMOR OF THE BRAIN. WITOLD GRABOWSKI, *Trav. d'Inst. d'anat. path. d. Univ. de Pologne* 1:487, 1925.

In this case two tumors were found in the brain of a 42 year old man. The larger, a soft, gray mass, 4 cm. in diameter, was in the right occipital lobe. It was closely attached to the choroid plexus and the ependyma of the lateral ventricle. The second was at the junction of the left frontal and parietal lobes.

Microscopic examination showed vascular connective tissue forming villi and covered with many layered epithelium. The epithelial cells showed atypical mitotic figures and other characteristics of cancer cells. At the connection with the wall of the ventricle tumor cells could be seen invading the brain tissue.

The close connection with the choroid plexus, the sharp separation of connective tissue and epithelium, the absence of glia cells, suggest that the tumor sprang from the epithelium of the choroid plexus. The atypical form of the cells, many mitotic figures, infiltration of the brain and the presence of the smaller metastatic tumor indicate a malignant epithelial tumor, of the variety of carcinoma.

B. R. LOVETT.

GIANT-CELL SARCOMA OF THE THYROID. H. SCHULZ, *Beitr. z. path. Anat. u. z. allg. Pathol.* 74:77, 1925.

Schulz describes a giant cell sarcoma of the thyroid, in which the giant cells were of two types. Some had multiple vesicular nuclei and were of the type to which the term parenchymatous tumor giant cells has been applied by others. The other type of cell was larger and contained a greater number of nuclei which were small, condensed and hyperchromatic; these suggest foreign body giant cells and were found especially in and about areas in which hemorrhage and necrosis had occurred. The author thinks it important to distinguish between progressive giant cells, whose vital functions are active, and regressive giant cells, whose vitality is low because of poor nutrition.

O. T. SCHULTZ.

XANTHOMA OF THE PERIOSTEUM. W. GAUHL, *Beitr. z. path. Anat. u. z. allg. Pathol.* 74:88, 1925.

Gauhl reports a spindle-cell xanthoma arising from the periosteum of the tibia of a woman aged 66. The cholesterol content of the blood was high, 435 mg. per hundred cubic centimeters of blood. Many of the tumor cells were swollen by the presence of doubly refractile lipid material and were transformed into typical xanthoma foam cells. In necrotic areas of the tumor cholesterol was deposited in crystalline form. Xanthoma is not a specific type of tumor, but is the result of lipid deposition in areas or cells the chemical condition of which is such as to favor deposition in individuals with cholesterolemia.

O. T. SCHULTZ.

Medicolegal Pathology

INVESTIGATION CONCERNING THE ORIGIN OF BLOOD SPOTS BY THE ISOHEMAG-GLUTINATION METHOD. ÉTIENNE MARTIN and A. ROCHAIX, *Ann. de méd. legale* 5:1, 1925.

By the absorption method it was found that the iso-agglutinin in a certain blood spot was different from the iso-agglutinin of the blood of the accused who had claimed that the spot was due to blood from a cut of his finger. At the time this examination was made it was not possible to demonstrate any agglutinin in extracts of the blood of the spot in question which was then several months old.

ELECTROCUTION WITH A CURRENT OF LOW TENSION. G. ROUSSELIÉ, *Ann. de méd. legale* 5:50, 1925.

In explanation of the death of two soldiers who were playing with an alternating current of 127 volts, the suggestion is made that the shocks with which they were amusing themselves finally induced sweating of the hands, and thereby lessened resistance for the current. The hands were found burned. This is additional evidence that low tension currents are not as harmless as has been supposed.

E. R. LECOUNT.

EXPERIMENTAL STUDY OF DEATH BY STRANGULATION. STEVANOVITCH, *Ann. de l'Inst. de méd. legale de l'Univ. de Lyon* 5, 1924-1925.

The force of compression is from in front and directed backward, the thyroid gland and structures about it suffering most. The carotid arteries, pneumogastric and sympathetic nerves are all compressed, and death may occur from reflex cardiac syncope or from asphyxia.

E. R. LECOUNT.

HEMORRHAGES IN THE LUNGS FROM TETRACHLORMETHANE. T. TAKASAKA, *Deutsche Ztschr. f. d. ges. gerschl. Med.* 6:488, 1925.

A marked hemoptysis observed in Japan in one patient led to experiments there with rabbits, which were continued in Berlin. In addition to the fatty changes of the parenchymatous organs found by others, extensive hemorrhages were met with in the lungs, and considerable hemolysis.

For two reasons, these results should cause no surprise, since in rabbits hemorrhages in the lungs are common from many causes, and the other poisons of which this is a member, poisons in which halides dominate, are known to produce hemorrhage, necrosis and fatty changes in many of the important viscera.

The doses used were considerable, 0.5 to 3.5 Gm. per kilogram, the alterations increasing with dosage and most with acute poisoning. It would be helpful in this instance, as in others in which the effects of poisons are studied, to determine the changes produced in other animals.

E. R. LECOUNT.

LONG-CONTINUED RIGOR MORTIS (?). G. STRASSMANN, *Deutsche Ztschr. f. d. ges. gerschl. Med.* 6:515, 1925.

Based on examination of unembalmed bodies exhumed some time after burial, doubt is expressed regarding the propriety of interpreting as due to rigor mortis the results of dehydration which bring about stiffness of joints, especially

those of the hands and feet with a shrinkage of the subcutaneous areolar and fatty tissues, muscles and fascia.

This postmortem drying may bring about various distortions of the body, such as bending of the knees up toward the abdomen or turning of the body toward one side. The rigidity may allow turning over or lifting up of small bodies, with little if any return to the straight position of burial.

E. R. LeCOUNT.

EXPERIMENTS WITH ELECTRICAL CURRENTS OF MODERATE AND HIGH VOLTAGE.

F. PIETRUSKY, *Deutsche Ztschr. f. d. ges. gerschtl. Med.* 6:535, 1925.

An account of the changes found in three bodies of men electrocuted and of a fourth killed by lightning, is presented, together with descriptions of those found in guinea-pigs killed with electricity.

An effort was made in the animal experiments to evaluate the several factors, voltage, amperage, time of subjection to the current and differences between constant and alternating currents. Only one periodicity, 50 per second, of alternating current, was employed. Consequently, this factor remained constant.

Moderate voltages of about 220 for both currents and amperages of 0.1 to 0.3 caused more damage and produced death more regularly than higher voltages of 2,500 to 30,000 and amperages of 1.2 to 3. One is left with the impression that a much wider range of experimentation is clearly indicated to estimate the importance of these factors.

There is not a great variety to the deep-seated alterations described, chiefly hemorrhages, and these sometimes in minute tears—notably in the myocardium; the lungs rather devoid of blood in some animals; marked changes in the blood, such as reduction to a minute meshwork containing crystals of blood pigment; hyperemia of viscera and more rarely necroses.

Some reference to the exceedingly varied character of the changes in the skin is made, and to the increased danger when a current of high is reduced to one of lower voltage, by sparking, and the ensuing burn of the skin. No mention is made of microscopic changes in the central nervous system. Again emphasis is placed on the necessity of having the current traverse the trunk so that the heart is involved if death is to be produced.

Artificial respiration, and preferably the Sylvester method, should be prolonged, since there are now records of a considerable number saved from certain death in this way.

E. R. LeCOUNT.

Society Transactions

THE MINNESOTA PATHOLOGICAL SOCIETY

MOSES BARRON, M.D., *President*

Dec. 15, 1925

PYOGENIC GRANULOMA: A CLINICAL AND HISTOLOGIC REVIEW. H. E. MICHELSON.

Dr. Michelson's report was based on a study of twenty-eight cases of pyogenic granuloma. These growths consist largely of granulation tissue in which the capillaries are prominent, and they are therefore sometimes confused histologically with angioma. They occur on the skin and mucous membranes. Both sessile and pedunculated forms occur, the former occurring more frequently on the palmar surfaces. The color is usually a shade of red. Ulceration is common. Sometimes there is a history of injury preceding the appearance of the growth. The tumors grow rapidly and soon reach a stationary size. There is some downward growth of the surface epithelium, and this fact, together with the clinical features, may lead to an erroneous diagnosis of squamous cell carcinoma. This error is especially likely to occur with granulomas on the lower lip. (This paper was published in full in *Arch. Dermat. & Syph.* **12**:492-505 [Oct.] 1925).

A CLINICAL AND HISTOLOGIC STUDY OF THE RETINAL VESSELS IN HYPERPIESIA. G. E. FAHR and W. E. CAMP.

The changes in the retinal blood vessels in hyperpiesia (essential hypertension) were discussed. A number of cases clinically which subsequently came to necropsy were studied. The type of renal disease was determined by postmortem examination in every case. It was found that one can distinguish chronic glomerulonephritis from hyperpiesia in about 90 per cent of the cases by examination of the eyegrounds. The most characteristic change in hyperpiesia in the early stage is narrowing of the retinal arterioles from uniform contraction. In the later stages the narrowing is present and the caliber of the vessels is uneven. Sections of the retina from two cases were demonstrated. The microscopic sections showed that the uneven narrowing of the arterioles was due to irregular subendothelial deposits of hyaline material.

RENAL INSUFFICIENCY IN PRIMARY HYPERTENSION. E. T. BELL.

Renal arteriolar sclerosis is present in varying degree in about 85 per cent of cases of primary hypertension, and in over 50 per cent the degree of involvement of the arterioles is such that it may be classified as severe. The pathologic change consists in a subendothelial deposit of hyaline material. Atrophy of the glomerulus ensues when the afferent arteriole becomes greatly narrowed or occluded. In about 10 per cent of cases of primary hypertension the atrophy of the renal parenchyma is extensive enough to produce a renal insufficiency that can be determined by functional tests, but death from uremia is rare. There is therefore no sharp separation to be made between primary hypertension

without renal insufficiency and that with renal insufficiency. The term "malignant hypertension" has no exact meaning.

Lantern slides were shown illustrating the various degrees of renal arteriolar sclerosis.

DEMONSTRATIONS OF INGUINAL GRANULOMA. E. E. B. FOLEY and J. F. NOBLE.

A clinical case of inguinal granuloma in a man about 40 years old was demonstrated. The growth covered the entire external genitalia anteriorly. A biopsy was made. One peculiarity of the case was that the Wassermann reaction was positive. Under antimony treatment the growth decreased somewhat in size. There was much greater decrease under antisypilitic treatment, but neither method of therapy caused the growth to disappear. Operative procedure was under consideration when the patient was last seen.

INGUINAL GRANULOMA. KANO IKEDA.

A woman, aged 59, unmarried, was admitted to the Minneapolis General Hospital, May 31, 1925. She first noticed a small pimple on the right labium about six months before. The lesion grew slowly until April, when it suddenly began to increase in size and soon broke open, draining a serous fluid. She also noticed a small swelling in the right inguinal region for several weeks. Recently, she had noticed foul smelling, slightly bloody vaginal discharge.

In her work, she used her right leg to run a machine, and this, she thought, irritated the region.

On inspection, there was a large mass involving the right labium major. It was about the size of a lemon, red and tender. The inner aspect of the labia showed a yellowish granular necrotic area about the size of a 50 cent piece. There was a foul odor. The contiguous lymph nodes on the right were enlarged and hard, but discrete. There were no enlarged nodes on the left side.

On June 4, the patient had a septic temperature. The leukocyte count was 26,500. There were occasional sudden sharp pains around the right side of the vulva, shooting down the leg. The mass appeared to be growing rapidly. A bluish indurated border preceded the ulceration, which was quickly spreading.

On June 9, the growth was as large as a fist. Ulceration was spreading rapidly.

On June 19, the growth was large.

On June 20, six radium needles, 12.5 mg. each, were inserted in the right groin, and one of 50 mg. in the primary mass.

On June 23, the entire necrotic growth was removed by cautery. Microscopically, a granulomatous growth was seen; it was not malignant.

On August 13, the patient had a lump on the left anterior chest. Roentgenograms showed swelling of the soft tissue. There were no lung changes. There was probably a metastatic nodule; biopsy was advised, but was not done.

The postoperative course was satisfactory. Purulent discharge from the wounds gradually decreased.

On September 3, the wounds were nearly healed. The patient was discharged as improved.

The tentative diagnosis was carcinoma of the right labium major with metastasis to the right inguinal glands.

Subsequently, numerous sections made from the mass removed showed extensive ulceration with a gangrenous base and chronic suppuration and abscesses

in the deeper tissue; the epidermis was hypertrophic, with deep and irregular papillary projections with edema and fibrosis of the papillae and corium. There was dense fibrosis in the deeper layer of the corium and subcutaneous area.

The patient was seen recently. She was in excellent condition subjectively; she had not lost in weight; she weighed about 160 pounds (72.6 Kg.); she was working every day. The wounds healed completely. There was a small induration in the original site of growth, but this was interpreted as a scar. The nodule in the left thoracic wall had disappeared. No recurrence of the inguinal adenopathy was noted.

Jan. 20, 1926

POSTOPERATIVE COLLAPSE OF LUNG. LEO G. RIGLER.

Following operation or trauma below the neck, a collapse of the lung frequently occurs. It is probably due to a combination of respiratory immobility and bronchial obstruction. Grossly, the lung is shrunken and airless, while on section the alveoli are seen to be obliterated by the collapse of the alveolar walls. The pathologic and clinical pictures are almost similar to the atelectasis which follows complete bronchial obstruction by a foreign body. This condition occurs most frequently after abdominal operations, but may follow trauma, such as bullet wounds or fractures.

The most prominent symptoms are dyspnea and pain; the most important signs are cyanosis, immobility of the chest, dullness and displacement of the mediastinum to the affected side. The most frequent mistaken diagnoses are pneumonia and pleural effusion. Pneumonia may occur as a complication. The roentgenogram offers the greatest diagnostic aid. The findings are opacity or mottling of the lung, a high diaphragm and displacement of the mediastinum toward the affected side. With the exception of complete bronchial obstruction by a foreign body, this is the only acute condition in which these signs occur. Three cases are reported in which the diagnosis was made roentgenologically. A search of the records of the Minneapolis General Hospital revealed six more cases. Of 285 cases of ordinary pneumonia in which there was adequate roentgen-ray study, two cases in which collapse had occurred were found. In forty-eight cases of post-operative or post-traumatic pulmonary complications, eight cases of massive collapse were found.

Four groups of cases are presented. The first includes three cases of uncomplicated unilateral collapse following abdominal operations. The second group consists of two cases of postoperative collapse in which pneumonia occurred as a complication. The third comprises three cases following fractures of the chest and pelvis. The last case followed a bullet wound and showed alternate collapse and clearing of the lung over a period of two months, with eventual complete recovery.

POSTPNEUMONIC COLLAPSE OF LUNG. T. A. PEPPARD.

Dr. Peppard presented the history with the clinical and roentgenologic findings of two cases of postpneumonic collapse of the lung. These were cases of ordinary lobar pneumonia. During the course of the disease, the physical and roentgenologic findings showed a marked displacement of the mediastinal structures to one side. Both patients recovered, and the mediastinal organs returned to their normal position.

DEMONSTRATION: EXPERIMENTAL POLIOMYELITIS IN MONKEY. J. C. MCKINLEY.

Dr. McKinley demonstrated a number of microscopic slides, showing the lesions of experimental poliomyelitis in monkeys. The virus was obtained from the Rockefeller Institute. The lesions in the central nervous system were practically identical with those of the human poliomyelitis.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Feb. 8, 1926

RUTH TUNNICLIFF, M.D., *President, in the Chair*

THE COMPARATIVE PATHOLOGY OF THYROID TUMORS. MAUD SLYE, HARRIET F. HOLMES and H. GIDEON WELLS.

A study of the literature on the occurrence of tumors of the thyroid in animals discloses that while malignant thyroid neoplasms are not uncommon in man, they seem to be extremely rare in all other animals except the dog family. In dogs the thyroid seems to be one of the commonest sites of cancer, and, furthermore, nearly all of the scanty number of cases of thyroid malignancy observed in wild animals have been observed in canines, chiefly wolves. A few cases have been observed in horses, but practically none in any of the domestic food animals. Only two cases have been reported in birds. A few cases have been reported in rats. A striking feature of thyroid cancer is that many of the growths show histologic characteristics suggesting in part carcinoma and in part sarcoma, and this is equally true for the cancers observed in the lower animals as well as in man. Hitherto no case of thyroid tumor seems to have been reported in mice. In about 51,700 necropsies in the Slye stock of mice there have been but seventeen animals in which noticeable enlargement of the thyroid was observed. Five of these had simple goiters. Twelve had malignant tumors, of which two seemed to be sarcomas and six carcinomas, and four exhibited mixed characteristics of sarcoma and carcinoma.

FUSOSPIROCHETAL ABSCESS OF THE TONSILS. I. PILOT.

In the consideration of tonsillar infections by *B. fusiformis* and Vincent's spirochete, the most common condition is the acute angina. These organisms can be demonstrated readily in large numbers in smears made from the membrane. A considerable number of persons (30 per cent or more) harbor in their tonsils granular, actinomyces-like masses, made up largely of these organisms. The presence of these granules excites little or no cellular reaction. A chronic inflammation may exist if the granules distend the crypts. In the course of routine examination of many hundreds of tonsils, chronic abscesses were often encountered, but in only three instances were the lesions associated with these organisms.

CASE 1.—The tonsils were equal in size, 2 cm. long, 1.7 cm. wide and 1.5 cm. thick. Under the capsule of one, a gray bulging occurred which on section proved to be an abscess 8 mm. in diameter, filled with foul smelling pus. Smears revealed numerous fusiform bacilli, spirochetes and cocci. Aerobic cultures contained *Streptococcus viridans* and the anaerobic streptococci together with fusiform bacilli. The opposite tonsil contained a smaller abscess under the

capsule, 5 mm. in diameter, filled with odorless pus. Smears revealed streptococci and no anaerobes. In microscopic sections of the putrid abscess, a chronic inflammatory reaction was present. The cavity was lined by an irregular, thin epithelium and filled with numerous leukocytes, débris and masses of bacteria. The capsule was markedly thickened, and contained small foci filled with leukocytes. In Levaditi preparations the bacilli and spirochetes appeared in the abscess wall.

CASE 2.—The tonsils measured 2 cm. long, 1 cm. wide and 1 cm. thick. On section there was a distinct increase in connective tissue and a dilated crypt filled with foul smelling pus. Smears revealed the anaerobes and cocci. The opposite tonsil had some purulent exudate in a crypt with no odor, although stained preparations contained a moderate number of fusiform bacilli and spirochetes.

The reaction in microscopic preparations was of a chronic inflammatory character with a distinct increase in connective tissue. In Levaditi preparations the bacilli and spirochetes formed masses in the exudate of the crypt, and only a few were found in the lining of the cavity.

CASE 3.—These were large tonsils, 2.5 cm. long, 1.5 cm. wide and 1.5 cm. thick. On section an abscess cavity filled with a foul exudate was found. Smears revealed a mixture of bacilli, spirochetes and cocci. In the microscopic sections a distinct abscess with marked necrosis of the wall was observed, communicating with a crypt. In Levaditi preparations the necrotic region was filled with many bacilli and spirochetes, but there was no invasion of the contiguous tissue.

A fourth instance was observed in a medical student who complained of recurrent sore throat with foul breath. His tonsils had been removed, but the sore throat persisted. On examination, there appeared considerable lymphoid tissue in the upper portion of the tonsillar fossa, with a foul purulent discharge oozing from the surface. A wire loop introduced into the region led into a small abscess cavity containing foul pus. Smears demonstrated numerous bacilli, spirochetes and cocci.

A chronic form of fusospirochetal infection of the tonsil is described. The exudate is usually foul smelling and contains streptococci in addition to the anaerobes. The lesion is a chronic abscess, and in one instance associated with necrosis of the tissue lining the abscess cavity.

TORSION OF THE LEFT FALLOPIAN TUBE WITH SPONTANEOUS AMPUTATION, AND FIBROMA OF THE RIGHT OVARY. C. W. BARRETT and A. F. LASH.

Spontaneous amputation of fallopian tubes, especially normal, is a rare post-mortem and operative finding. Twenty-seven cases have been observed post-mortem, the first being that of Morgagni, 1748. After operative procedures were undertaken, surgical reports followed, and since the first in 1892 by Martin, twenty-three have been recorded. The interpretation of the mechanism in the individual cases is interesting.

The incidence of fibroma of the ovary is 1.3 to 2 per cent of ovarian tumors. Shochet found eighty reports in the literature up to 1924. It is of no clinical significance except when pressing on surrounding structures or when it is malignant. This report is made because of the rarity.

E. M., a white woman, aged 40, entered the gynecologic service of Dr. Channing W. Barrett at Cook County Hospital on Oct. 13, 1925. She com-

plained of pain in the lower part of the abdomen and of leukorrhea. The onset and course was as follows: While preparing breakfast on Oct. 10, 1925 (three days before admission), she had suddenly a severe knifelike pain in the left lower part of the abdomen. She went to bed and remained there the entire day. The pain gradually subsided after several hours, and became dull and aching. She vomited three times shortly after the onset of the pain. The next day she was able to get up and about, although the pain continued. Hot water bag relieved the pain a little. There was also painful urination, backache and loss of appetite. The leukorrhea, present for one year, was profuse. Her general systemic condition was good.

Menses began at the age of 12, twenty-eight day type, four day period, the last period being September 26 to 30, 1925. She married at the age of 19, had one full term pregnancy with spontaneous delivery. She married again at the age of 28, after divorcing her husband. A full term pregnancy with spontaneous delivery followed. A third pregnancy terminated at the third month by abortion, which was completed by a curettage. Following this operation she had fever and was confined to bed for two weeks.

By physical examination were found a slight tenderness in the iliac fossae, a relaxed pelvic floor with a cystocele and a rectocele, and a prolapsing uterus with adnexitis. A vaginal hysterectomy, pelvic floor repair and removal of the tumor of the right ovary by laparotomy was done.

The tissue contained the uterus, two fallopian tubes and a right ovarian tumor. The uterus was 6 cm. long, 5 cm. wide and 5.5 cm. thick. The peritoneum was smooth and glistening. The fundus had the normal rounded form and from the left cornua extended the conical stump of the left fallopian tube, which was soft, 1 cm. in length. The uterine wall was 1.6 cm. thick, and the myometrium was firm. The endometrium was normal in appearance and thickness. The cervix at the external os was firm and nodular from the multiple healed lacerations and nabothian cysts. The endocervix was smooth and covered with clear mucus.

The left fallopian tube was a bluish-black, twisted mass. The length of the tube was 12.5 cm., and the diameter varied from 2 mm. at its conical uterine end to 2 cm. at the fimbriated end. The peritoneal surface was smooth and the tube was firm. The uterine end was closed and conical, while the fimbriated end was open. Longitudinal section of the tube revealed a thick, dark red wall, the lumen filled with clotted blood and the longitudinal folds visible after removing some of the blood. The vessels in the part of the mesosalpinx attached to the tube were thrombosed.

The right fallopian tube was 12 cm. long and 1 to 2.5 cm. in diameter. It was firm, thick and bound together by adhesions, but the fimbriated end was open. The endosalpinx was unchanged.

The tumor representing the right ovary was hard, smooth, round, flattened anteroposteriorly 6 cm. in diameter and 4 cm. thick. The surfaces made by cutting were firm, white fibrous tissue.

In microscopic sections of the spontaneously amputated tube there was a recent hemorrhage without inflammation. The muscular fibers of the wall were separated by masses of red blood cells and edema, while the vessels were markedly dilated. In the endosalpinx the infiltration with blood cells was marked.

Microscopic sections of the corpus showed the endometrium to be in the resting stage. Both endometrium and myometrium were hyperemic. There

were masses of leukocytes in some of the glands. In one subperitoneal region there was some edematous fibrous tissue with a mass of leukocytes.

The tumor of the ovary contained only spindle-shaped connective tissue cells of the uniform shape and staining qualities.

The tissue changes in this patient, then, were a fibroma of the right ovary, healed right perisalpingitis and spontaneous amputation of the normal left fallopian tube, into which there was a recent hemorrhage, resulting from torsion. In this instance, the spontaneous amputation of the tube was certain as there was no history or evidence of operation in these tissues, and the twisted tube was further confirmation. However, to interpret the mechanism which produced the torsion and spontaneous amputation requires further study.

Constipation produced congestion in the pelvis which, according to Payr's hemodynamic theory, may initiate a twisting of an organ with a pedicle. Further, the prolapsing uterus brought the left cornua at a level or below that of the infundibulopelvic ligament, thereby narrowing the width of the broad ligament or pedicle. Thus the twisting of the congested tube on its narrowed pedicle could be increased by mechanical forces (bending or twisting of the body as a whole, or a blow to the abdomen), until amputation occurred. Spontaneous amputation secondary to torsion was observed also by Rokitsansky and Praeger.

PRIMARY ACUTE AORTITIS. B. Z. RAPPAPORT.

Primary acute aortitis is a rare condition. Only ten cases have been reported (Stumpf: *Ergebn. d. allg. path. u. path. Anat.*, 1913, p. 56). Aortitis secondary to adjacent mediastinal infection or to aortic endocarditis is a more common condition.

A man, aged 47, with a syphilitic infection twenty years previously, and a positive blood Wassermann reaction, was admitted to Dr. Williamson's service at the Illinois Research and Educational Hospital. His complaints were due to cardiac decompensation of eighteen months' duration, worse during the last five weeks. The physical findings were those of cardiac decompensation and an enlarged heart, a systolic murmur over the apex and a diastolic murmur over the sternum. The blood pressure was 175 systolic and 70 diastolic. The temperature was normal. The patient died sixteen days after admission.

The necropsy by Dr. R. H. Jaffé was limited to an abdominal incision. There were recent infarcts of the lungs, hyperemia of the kidneys and the liver, and in the thoracic aorta a syphilitic sclerosis. In addition, there were five or six yellow plaques 2 to 3 mm. in diameter just above the aortic cusps. No changes suggestive of a healed or recent endocarditis were found. The heart was markedly enlarged.

Microscopic examination of the aorta demonstrated the usual tissue changes characteristic of syphilis, and also an acute inflammation. Miliary abscesses composed of polymorphonuclear leukocytes in and about regions of necrosis were present in the media and between the intima and media pushing the former layer toward the aortic lumen. The elastic fibers were destroyed in these places. Gram-positive streptococci and diplococci were found. In some regions hyaline bodies, described as Russel or fuchsin bodies, were present. Cultures of the blood at necropsy contained a green producing streptococcus. The mode of infection was considered hematogenous from a focus not demonstrated by the necropsy. The preexisting syphilitic changes of the aorta were considered the predisposing cause in diminishing the local resistance to infection.

DISCUSSION

DR. H. G. WELLS: When examining sections from cerebral and coronary arteries, the site of fatal thrombosis, I have been impressed with the frequency with which the sclerotic lesions, whether syphilitic or senile, on which the thrombosis has taken place, have shown histologic evidence of acute inflammatory processes. This has suggested to me that the common fatal accident of cerebral and coronary thrombosis is frequently the result of lodgment, in these areas of tissue injury in the arteries, of pathogenic bacteria circulating in the blood. Without such a superimposed infection of the sclerotic patches the thrombosis might not have occurred.

DR. R. H. JAFFÉ: I am especially interested in Dr. Well's statement. During and after the great pandemic of influenza in 1918 I made the observation that a relatively large number of middle-aged persons had died suddenly from coronary thrombosis. The changes in the walls of the coronary vessels were slight, and did not exceed those usually found in persons above 45 years of age.

With regard to Dr. Rappaport's case, I should like to say that the chronic syphilitic changes in the media and adventitia of the aorta seemed not to be affected by the acute purulent process in the intima.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Feb. 11, 1926

EUGENE L. OPIE, M.D., *Presiding*

REVERSIBLE AND IRREVERSIBLE SWELLING OF LIVING AND DEAD CELLS. BALDWIN LUCKE and MORTON McCUTCHEON. (From the Laboratory of Pathology, University of Pennsylvania Medical School.)

One of the fundamental properties of animal cells is their ability to undergo increase in volume under certain conditions. In addition to such normal processes as growth and increased function, certain pathologic states lead to swelling of tissue cells. Cloudy swelling, hydropic degeneration and coagulation necrosis are conditions of abnormal volume increase well known to pathologists. Among the factors capable of producing such changes, acutely acting toxic substances are believed to be important. The mechanism of the action of such substances remains obscure, in spite of numerous studies employing the usual histologic procedures of fixation and staining, as well as a smaller number of investigations on cells isolated from living animals. The latter type of study has failed to show whether cells were alive or dead at the end of the experiment. Yet this is a question of fundamental importance to the general pathologist. It would be of great interest to know whether cells that have undergone swelling as the result of poisoning are capable of returning to their normal state, or whether they have been permanently damaged, perhaps even killed.

The purpose of the present investigation was to determine whether animal cells swollen as the result of the action of injurious agencies return to normal size when the injurious agent is removed, or whether irreversible changes have occurred. For such a study, marine ova possess great advantages, since they can be isolated and studied in their normal environment, sea water,

therefore without injury other than that induced by the experimental agents employed. At the end of the experiment, injury effects can be demonstrated by addition of sperm. Uninjured cells then undergo cleavage, whereas the development of injured cells tends to be atypical, and dead cells of course show no division. The ova of the sea urchin, *Arbacia*, are particularly favorable material, since they are in general spherical, and can therefore be accurately measured by an ocular micrometer.

It was found that reversible swelling occurred only when the cells were exposed to hypotonic sea water, i. e., sea water diluted with distilled water. All other agents which produced swelling were irreversible in their effects. The ova did not return to normal size when subsequently placed in a normal environment. By the method of centrifugation, it was found that such cells had suffered an increase in viscosity which indicated coagulation. Further, addition of sperm failed to produce cleavage, indicating severe injury or death, which appeared to accompany or rather to precede increase in volume.

The degree of swelling was found to be proportional to the concentration of the agent employed and to the length of exposure. Heat acted in this way, as did dilute hydrochloric and salicylic acids dissolved in sea water. Ether, above low concentrations, produced rapid irreversible swelling. Carbonic acid, in amounts soluble in sea water, produced little volume change though eventually killing the cells. Other agents extremely toxic to mammalian cells, such as atropine and bacterial toxins, were comparatively harmless to *Arbacia* eggs.

These experiments show in a clear-cut way that the various agents that produced swelling, except hypotonic solutions, were irreversible in their effects, and killed the ova. It is hoped hereafter to determine whether the same principles apply to tissue cells.

AN INVESTIGATION OF GYE'S WORK ON THE ETIOLOGY OF MALIGNANT TUMORS.

MALCOLM J. HARKINS, JAY FRANK SCHAMBERG, JOHN A. KOLMER. (From the Research Institute of Cutaneous Medicine, Philadelphia.)

This article will be published in full in the *Journal of Cancer Research*.

In July, 1925, Dr. W. E. Gye (*Lancet* 2:109, 1925) published an article entitled "The Etiology of Malignant New Growths." From his investigations Gye concludes that all malignant new growths contain an ultramicroscopic organism or virus and an activating substance which he designates the "specific factor," which "ruptures the cell defenses" and enables the virus to infect.

In our investigations, we attempted to confirm the cultivation of the virus in vitro and to demonstrate the so-called "specific factor," adhering strictly to the procedures outlined by Gye. We used, as did Gye, the Rous chicken sarcoma, no. 1, a spindle cell sarcoma, morphologically resembling mammalian sarcoma, but it can be transferred from chicken to chicken by cell-free Berkefeld filtrates.

Of twenty-two attempts to obtain cultures free of contaminating organisms directly from the tumor, seven were successful. These are called the "primary cultures" and always produced tumors when injected into chickens.

Further subcultures of these seven "primary cultures" were made, ranging from the third to the thirteenth generation. All cultures were incubated anaerobically. A total of 261 chickens were used in all the experiments.

As the crux of Gye's hypothesis revolves about the so-called "specific factor," especial attention was given its preparation. It is a sand and paper pulp filtrate of tumor suspension, to 10 cc. of which is added "a few drops

of chloroform," which according to Gye is supposed to destroy the virus. In all we prepared fifty-nine "specific factors" ranging in chloroform concentration from 5-6 drops to 1, 1.5, 2, 2.5, 3, 5, 10 and 20 per cent.

From our experiment it cannot be said that we succeeded in sterilizing "specific factors" with any degree of uniformity and assurance with amounts of chloroform up to 5 per cent, demonstrating the difficulty or rather the impossibility of preparing a noninfectious "specific factor" unless a concentration of chloroform greater than that stated by Gye is used.

In no instance was a tumor produced among thirty-five chickens receiving injections alone with different subcultures, nor when the "specific factor" failed to produce a tumor did a combination of "specific factor" and subculture virus produce one.

Our investigations do not confirm evidence of growth of the virus of the Rous chicken sarcoma in subcultures and suggest that the "specific factor" is in reality nothing more than a suspension of attenuated living virus which may or may not produce a tumor, depending on the fowl's susceptibility or resistance.

CONCERNING IMMUNOLOGIC STRAINS OF SPIROCHAETA PALLIDA. JOHN A. KOLMER, DOROTHY WILKES-WEISS and CAROLA E. RICHTER. (From the Research Institute of Cutaneous Medicine, Philadelphia.)

By means of cross agglutination and complement-fixation tests with the serums of rabbits immunized with intravenous injections of six different cultures of *Spirochaeta pallida*, no immunologic evidence of specific strains was observed. The results gave some confirmation to the view that so far as experimental syphilis of the rabbit is concerned, the localization of *Sp. pallida* and the subsequent course of the disease are largely influenced by the virulence of the organism and method of inoculation, as well as by the susceptibility of the host and the efficiency of its defensive mechanism. Probably the same or similar factors are operative in syphilis of human beings without involving the question of strain specificity or "selective tissue affinity" of the infecting spirochetes.

This article will be published in full in *The Journal of Infectious Diseases*.

Book Reviews

IMMUNOLOGICAL STUDIES. Edited by CARL H. BROWNING, Professor of Bacteriology in the University, and Director of the Laboratory, Western Infirmary, Glasgow. M. KOSAKI, T. J. MACKIE, T. TANIGUCHI, G. H. WILSON, N. YOSHINARE, co-authors. Cloth. Price, \$4.50. Pp. 239. New York: William Wood & Company, 1925.

This book is a compilation of the results of work by the authors, and is chiefly a rearrangement of published articles, although some new matter has been added. While it is stated that the humoral aspects of immunity are dealt with, the book, except for one chapter on opsonic action, is devoted to hemolysins. The introduction discusses antibody action in general, but again immune hemolysins are described to illustrate general phenomena. In the first chapter are given results of experiments with globin as an antigen which are remarkable because previously no one had found this protein to be antigenic. Complement fixations are obtained with a high degree of specificity. Antiglobin serum does not react with serum from the same species nor with the hemoglobin from which the globin was obtained; neither does it contain lysins for homologous red cells; there is a chemical specificity as it reacts with globin from other species, although some paradoxical results are reported which await explanation. Different from most serologic reactions, optimum complement fixation occurs in an acid medium. No experiments with precipitins are given. The chapter on Forssmann's heterophile antigen and antibody, which is longer than any other, emphasizes the important rôle that the lipoids play in this phenomenon. It has been believed that normal hemolysins have a different structure from immune hemolysins, because heating to 56 C. to demonstrate their dual nature (amboceptor and complement) caused their complete disappearance. It is shown here, by removing complement by Berkefeld filtration, that the two antibodies operate in the same manner, but that normal hemolysins appear to differ from the immune in that they are thermolabile, have a feeble affinity for red cells and are interfered with by certain substances in serum. It is also demonstrated that conglutinin and hemolysin in ox serum are wholly independent properties which can be separated. The findings of Coca that red cells treated with osmic acid remove hemolysins nonspecifically from a serum are confirmed. An analysis of this phenomenon leads to the suggestion that osmic acid alters the surface character of red cell stromas so that they act on those constituents of serum with which the immune body is associated. Other interesting observations are that hemolytic immune body formed early in immunization, called immature antibody, shows qualitative differences from that formed later, one of which is the inability of multiple doses to effect an increase in the absorption of complement; normal opsonin is thermolabile and requires complement, while immune opsonin is thermostable and acts independently of complement; complement, in addition to mid-piece and end-piece, contains a "third component"; these three components, from whatever source isolated, can be recombined to produce complement action; the substance in fresh serum which complements immune hemolysin is different from that which complements venom hemolysin. The book is noteworthy in the use made of chemical procedures in the analysis of immune phenomena. The style is that of the ordinary scientific paper, and often the description of experiments is not clear. It is useful to the worker in immunity because it gives continuity to the work of the authors with useful suggestions and ideas.

THE INTERNAL SECRETIONS OF THE SEX GLANDS; THE PROBLEM OF THE "PUBERTY GLAND." By ALEXANDER LIPSCHÜTZ, M.D., Professor of Physiology in Dorpat University (Estonia). Price, \$6. Pp. 513, with over 140 illustrations. Baltimore: Williams and Wilkins Company, 1924.

The author, a physiologist of repute, undertakes in this volume a critical and exhaustive review of recorded experiments and hypotheses concerning the internal secretions of the sex glands in man, as well as in other animals.

For this task he is obviously equipped with an extensive acquaintance with the experimental work of others, to which he has added original observations; but he displays also limited acquaintance with research in human pathology which answers certain questions undecided by animal experimentation. It is illuminating that he is misled by the term "seminal vesicles" into confusing the purely secretory structures so-called in quadrupeds, which are, like Cowper's glands, independent in origin and outlet from the vas deferens, with the human seminal vesicle, a diverticulum of the vas deferens. On this mistaken conception he follows Steinach in transferring to man conclusions based on the removal of the so-called vesicles in quadrupeds; but the removal of the human seminal vesicles—a recognized surgical procedure—is apparently unknown to him.

In his interpretation of facts he seems at times unable to emancipate himself from earlier conceptions; for example, in former years he adopted Ancel and Bouin's doctrine that masculinity emanates solely from the interstitial (Leydig) cells of the testis; he endorsed Steinach's designation of these as the "puberty gland," and he accepted the latter's "rejuvenation" through hypertrophy of these glands alleged to follow occlusion of the outlet duct of the testis. He is now apparently convinced that these doctrines are erroneous, but convinced against his will.

Much space is given to the support of the hypothesis, adopted by the author as his own in 1919, that the soma of the embryo is asexual, the subsequent development of sex characters being brought about by the sex specific secretion of testis or ovary; just what determines the differentiation of testis or ovary is not quite clear. This theory, of course, fails to explain the authentic cases of human beings, typically feminine in mind and body, but possessing testes instead of ovaries; and men with ovaries but no testes. The hypothesis is confronted also by the bird, masculine in one lateral half, feminine in the other, but possessing only a testis; and by the mature egg-laying hen transformed into a sperm-producing cock.

The book is a valuable compend of pertinent literature worthy of careful perusal by physicians and physiologists alike, for its wealth of facts and its bibliography. The interpretation of these facts seems scarcely compatible with the conceptions of unbiased investigators—compare "The Biology of the Mammalian Testis and Scrotum," by C. R. Moore, *Quarterly Review of Biology*, January, 1926.

BONE SARCOMA. AN INTERPRETATION OF THE NOMENCLATURE USED BY THE COMMITTEE ON THE REGISTRY OF BONE SARCOMA OF THE AMERICAN COLLEGE OF SURGEONS. By E. A. CODMAN, M.D. Pp. 93, with 24 illustrations. New York: Paul B. Hoeber, 1925.

For several years, Dr. Codman has served as registrar for a committee of the American College of Surgeons on the registry of bone sarcoma. Many surgeons have filed the clinical history, one or more roentgenograms and at least one microscopic slide of such tumors. The material from each case has been examined and diagnosed by several pathologists. A tentative nomen-

clature has been adopted. On the basis of this collection, the author has undertaken to explain and illustrate the separate clinical entities commonly included as tumors of the bones. The title of the volume might more appropriately be "Bone Tumors" rather than "Bone Sarcoma."

The eight clinical entities recommended for recognition are as follows: (1) metastatic tumors; (2) periosteal fibrosarcoma; (3) osteogenic tumors, benign (osteoma, chondroma, etc.) and malignant (osteogenic sarcoma); (4) inflammatory conditions; (5) benign giant cell tumor; (6) angioma; (7) Ewing's tumor; (8) myeloma. The several types are clearly explained and illustrated by typical cases.

The little volume should be welcomed by all who are interested in diseases of the bones, since it is a faithful effort to standardize the nomenclature and sharpen our conceptions of the various entities.

It is pointed out that such terms as osteosarcoma, chondrosarcoma and myxosarcoma and their combinations should be replaced by the term "osteogenic sarcoma," since these descriptive histologic terms merely represent variations in structure of a sarcoma and not different kinds of sarcoma.

As admitted by the author, the new nomenclature is not perfect and perhaps should be revised in minor details before it is finally adopted. As regards the group "periosteal sarcoma," at least one member of the committee thought that this had been defined by agreement as an osteogenic tumor growing from the periosteum, which has the structure of a fibrosarcoma, i. e., a sarcoma of low malignancy with many fibers among its cells.

The term "parosteal sarcoma" might well be employed for sarcomas of the fascia lying adjacent to a bone.

The term "osteitis fibrosa" is used by the author in a much wider sense than by the majority of pathologists.

Dr. Codman has summarized the labors of his committee in a concise and readable way, and his efforts no doubt will be appreciated.

SCHISTOSOMIASIS VEL BILHARZIASIS. By C. G. KAY SHARP, M.D., Chief Medical Officer, Education Department Province of Natal Major R. A. M. C. (T. A.), with a Foreword by J. B. CHRISTOPHERSON, C.M.G., M.D., F.R.C.P., F.R.C.S. Price \$2.75. Pp. 74. New York, William Wood & Company, 1925.

This booklet will be of interest and value to any one who deals with problems of schistosomiasis. A good description is given of the stages in the development of the trematodes of the disease, the urinary form of which is the commonest in Natal, where the author has collected records of several hundred cases in the schools and where the coastal waters contain infected snails. In examining the urine the author proceeds as follows: After brief centrifugation of the urine, the fluid part is poured off and warm water (about 49 C. [120 F.]) is added; the suspension is centrifugated again in order to wash the eggs, the water poured off and new warm water added. The mixture is now allowed to stand for a time to permit the eggs to hatch, which can be watched under the low power of the microscope.

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